Title of Invention: Histone Deacetylase inhibitors ...

Inventors (please provide full names): See attached B.B sheet

Earliest Priority Date: See attached B.B sheet

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be sea elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utili Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

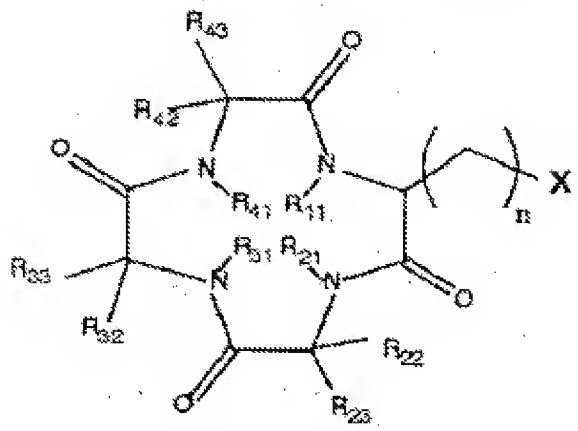
For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numb appropriate serial number.*

Structure search

Please search the genus of claim 1.

" " compounds of claim 2.

1. A compound represented by formula (1)



(1)

wherein

R_{11}, R_{21}, R_{31}, and R_{41} independently represent a hydrogen or methyl group;

R_{22}, R_{23}, R_{32}, R_{33}, R_{42}, and R_{43} independently represent any one of hydrogen, a linear alkyl group comprising 1 to 6 carbons, a linear alkyl group comprising 1 to 6 carbons to which a non-aromatic cyclic alkyl group or a substituted or unsubstituted aromatic ring is attached, a non-aromatic cyclic alkyl group, or a non-aromatic cyclic alkyl group to which a non-aromatic cyclic alkyl group or a substituted or unsubstituted aromatic ring is attached;

R_{21} and R_{22}, R_{22} and R_{23}, R_{31} and R_{32}, R_{32} and R_{33}, R_{41} and R_{42}, and R_{42} and R_{43} may independently represent a non-cyclic structure without bonding to each other, or may independently represent a cyclic structure by bonding to each other through a linear alkylene group having a chain length of 1 to 5 carbons, a linear alkylene chain having a chain length of 1 to 5 carbons and carrying a branched chain of 1 to 6 carbon atoms, or a linear alkylene chain having a chain length of 1 to 5 carbons and carrying a cyclic structure of 1 to 6 carbon atoms;

n can be selected from a range of numbers that enable the compound to have HDAC inhibitory activity; and

X represents a structural component having a structure that can coordinate with the zinc positioned at the active center of histone deacetylase.

******* INVENTOR RESULTS *******

```
=> d his l12

     (FILE 'HCAPLUS' ENTERED AT 15:37:37 ON 04 FEB 2009)
L12            4 S ((L10 OR L11) AND L8) OR (L8 AND L9)

=> d que l12
L1               STR
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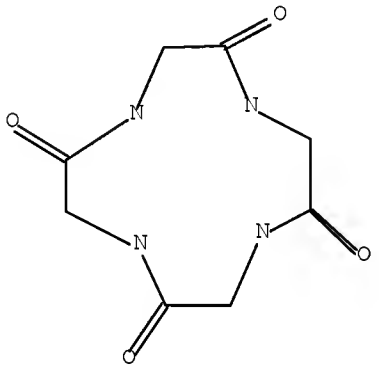
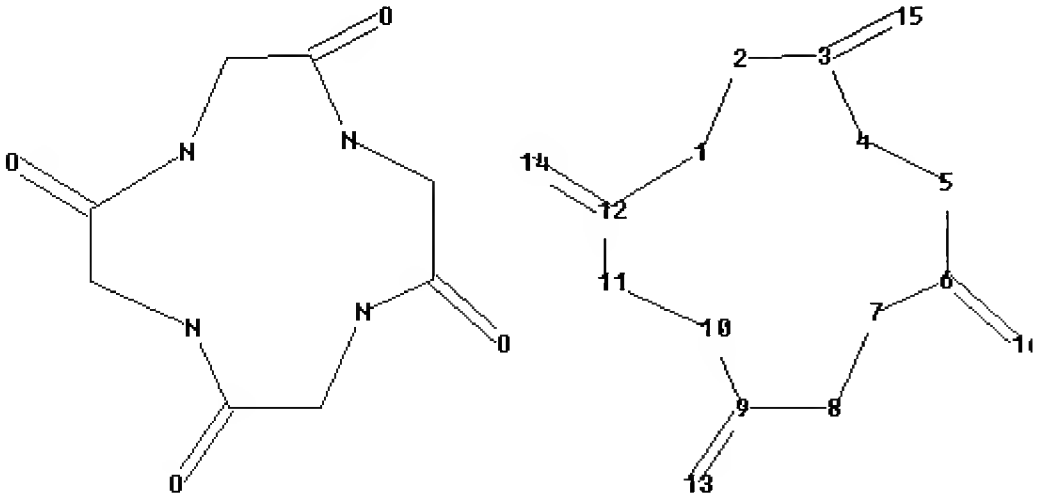


Structure attributes must be viewed using STN Express query preparation:

Uploading L2.str



```
chain nodes :
13  14  15  16
ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12
chain bonds :
```

3-15 6-16 9-13 12-14
ring bonds :
1-2 1-12 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12
exact/norm bonds :
1-2 1-12 2-3 3-4 3-15 4-5 5-6 6-7 6-16 7-8 8-9 9-10 9-13 10-11 11-12
12-14

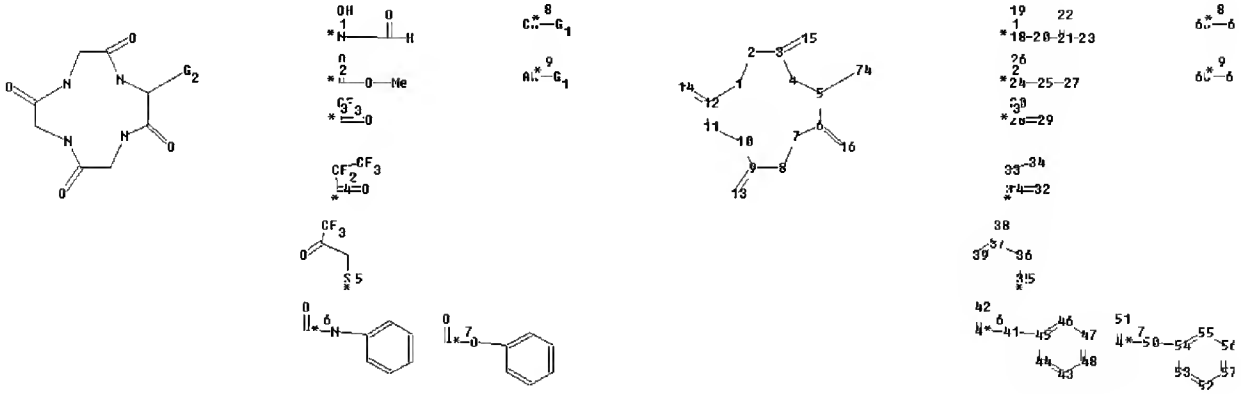
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 16:CLASS

L3 1852 SEA FILE=REGISTRY SSS FUL L1
L4 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation:

Uploading L4.str



chain nodes :
13 14 15 16 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
35 36 37 38 39 40 41 42 49 50 51 66 67 68 69 74
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 43 44 45 46 47 48 52 53 54 55 56
57
chain bonds :
3-15 5-74 6-16 9-13 12-14 18-19 18-20 20-21 21-22 21-23 24-25 24-26 25-
27
28-29 28-30 31-32 31-33 33-34 35-36 36-37 37-38 37-39 40-41 40-42 41-45
49-50 49-51
50-54 66-67 68-69
ring bonds :
1-2 1-12 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 43-44 43-48 44-
45
45-46 46-47 47-48 52-53 52-57 53-54 54-55 55-56 56-57
exact/norm bonds :
1-2 1-12 2-3 3-4 3-15 4-5 5-6 5-74 6-7 6-16 7-8 8-9 9-10 9-13 10-11
11-12 12-14 18-19 18-20 21-22 24-25 24-26 28-29 31-32 35-36 37-39 40-41

```
40-42  41-45
49-50  49-51  50-54  66-67  68-69
exact bonds :
20-21  21-23  25-27  28-30  31-33  33-34  36-37  37-38
normalized bonds :
43-44  43-48  44-45  45-46  46-47  47-48  52-53  52-57  53-54  54-55  55-56  56-57

isolated ring systems :
containing 43 : 52 :


G1:[*1],[*2],[*3],[*4],[*5],[*6],[*7]

G2:[*8],[*9]

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:CLASS  14:CLASS  15:CLASS  16:CLASS  18:CLASS  19:CLASS
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51:CLASS  52:Atom
53:Atom  54:Atom  55:Atom  56:Atom  57:Atom  66:CLASS  67:CLASS  68:CLASS  69:CLASS
74:CLASS




L6           35 SEA FILE=REGISTRY SUB=L3 SSS FUL L4
L8           16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6
L9            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US20070185071/PN
L10       14504 SEA FILE=HCAPLUS ABB=ON  PLU=ON  YOSHIDA M?/AU
L11         618 SEA FILE=HCAPLUS ABB=ON  PLU=ON  NISHINO N?/AU
L12           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L10 OR L11) AND L8) OR (L8
                AND L9)


=> d l12 1-4 ibib abs hitstr

L12  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:319633  HCAPLUS  Full-text
DOCUMENT NUMBER:          148:347312
TITLE:                    Compound having inhibitory activity on histone
                          deacetylase, and pharmaceutical comprising the
                          compound as active ingredient
INVENTOR(S):              Nishino, Norikazu; Yoshida, Minoru
                          ; Nakagawa, Junichi
PATENT ASSIGNEE(S):       Kyushu Institute of Technology, Japan; Riken Corp.
SOURCE:                   PCT Int. Appl., 55pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
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WO 2008029565	A1	20080313	WO 2007-JP64873	20070730
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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
JP 2008143886	A	20080626	JP 2007-223434	20070830
PRIORITY APPLN. INFO.:			JP 2006-239901 A	20060905
OTHER SOURCE(S):	MARPAT 148:347312			

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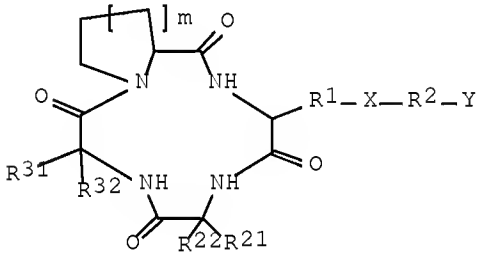


I

AB Disclosed is a novel compound having an inhibitory activity on histone deacetylase, which comprises a cyclic tetrapeptide derivative represented by the general formula (I). Also disclosed is a pharmaceutical comprising the compound as an active ingredient; I; wherein the cyclic tetrapeptide moiety is a known structure; R1 and R2 independently represents an alkylene group which may have a branch having 1 to 6 carbon atoms; X represents a group selected from -CO-, -O-, -S- and -SO-; R21, R22, R31, and R32 represent H, C1-6-linear alkyl, C3-6-branched alkyl, etc.; n represents 1 or 2; Y represents hydrogen, halogen, Ph group (including a substituted form), a pyridyl group (including a substituted form), an alkyl group having 1 to 6 carbon atoms (including a halogen-substituted form, with the groups described below), an alkyloxy group having 1 to 6 carbon atoms, an alkylcarbonyl group having 1 to 6 carbon atoms, an alkyloxycarbonyl group having 1 to 6 carbon atoms, an alkylthio group having 1 to 6 carbon atoms, an alkylthiocarbonyl group having 1 to 6 carbon atoms or a mono- or di-alkylamino group having 1 to 6 carbon atoms, provided that, when Y represents a Ph group (including a substituted form) or a pyridyl group (including a substituted form), Y may have a cyclic structure bound to R2.

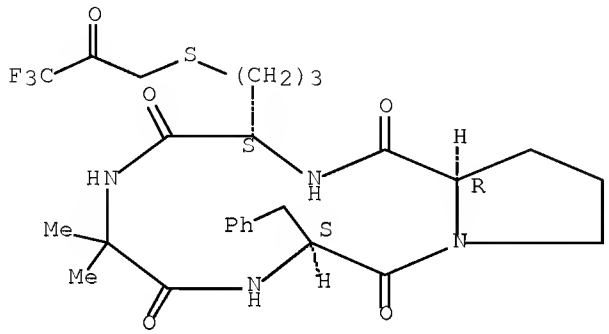
IT 931426-95-8P 931426-96-9P 931426-97-0P
1011725-77-1P 1011725-78-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(cyclic tetrapeptide derivs. having inhibitory activity on histone deacetylase, and antitumor pharmaceuticals comprising the derivs. as active ingredients)

RN 931426-95-8 HCAPLUS

CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalyl] (CA INDEX NAME)

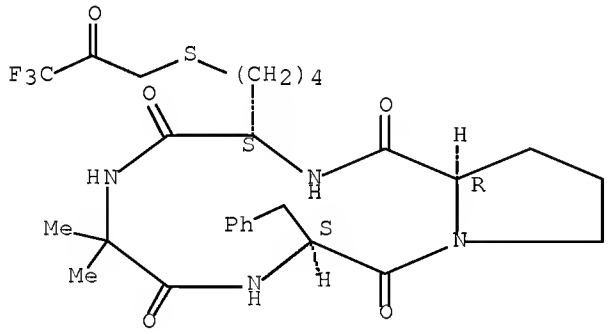
Absolute stereochemistry.



RN 931426-96-9 HCAPLUS

CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-6-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norleucyl] (CA INDEX NAME)

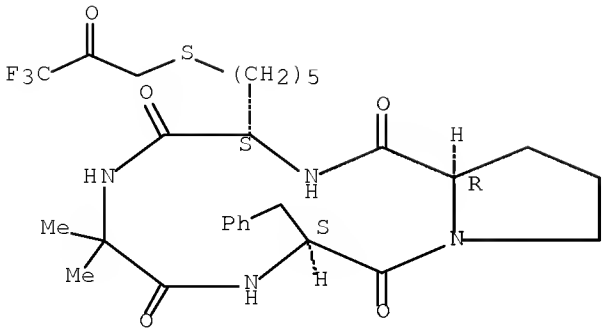
Absolute stereochemistry.



RN 931426-97-0 HCAPLUS

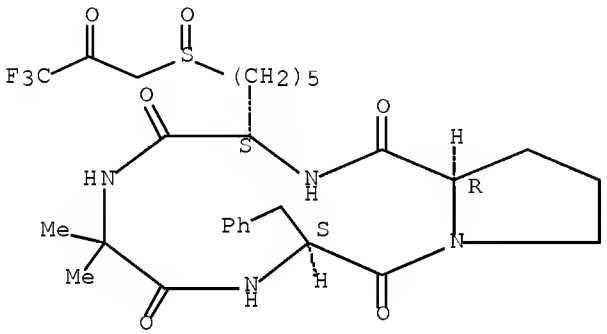
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S)-2-amino-7-[(3,3,3-trifluoro-2-oxopropyl)thio]heptanoyl] (CA INDEX NAME)

Absolute stereochemistry.



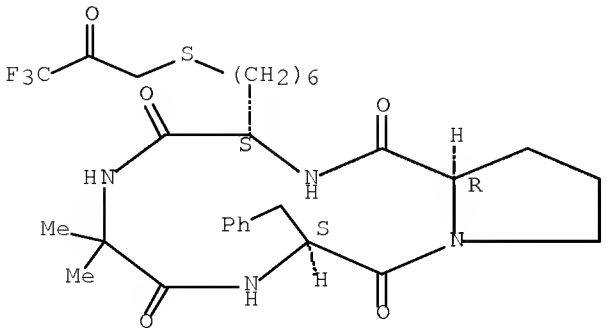
RN 1011725-77-1 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S)-2-amino-7-[(3,3,3-trifluoro-2-oxopropyl)sulfinyl]heptanoyl] (CA INDEX NAME)

Absolute stereochemistry.



RN 1011725-78-2 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S)-2-amino-8-[(3,3,3-trifluoro-2-oxopropyl)thio]octanoyl] (CA INDEX NAME)

Absolute stereochemistry.

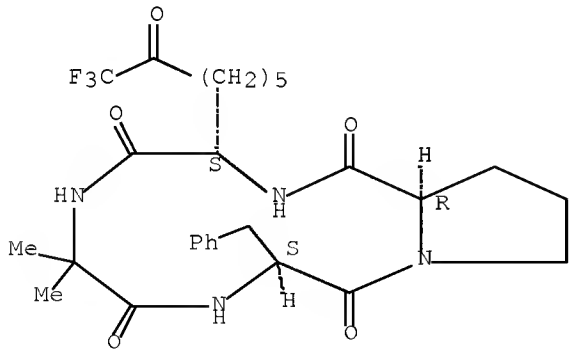


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

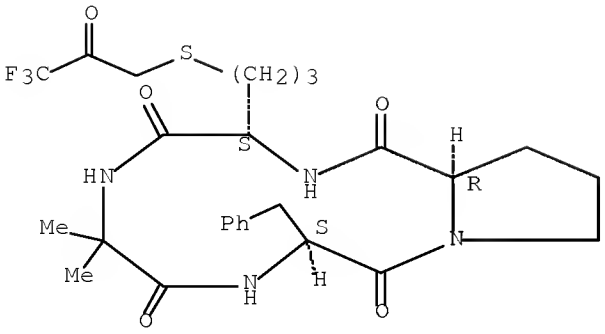
L12 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:505978 HCAPLUS Full-text
DOCUMENT NUMBER: 146:380274
TITLE: Design and synthesis of histone deacetylase inhibitors containing trifluoromethylketone moiety as the functional group
AUTHOR(S): Hirashima, Yoshinori; Kato, Tamaki; Nishino, Norikazu; Nishino, Tomonori G.; Yoshida, Minoru
CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan
SOURCE: Peptide Science (2006), Volume Date 2005, 42nd, 141-144
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Japanese Peptide Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:380274
AB A symposium report. Evaluation by human HDAC inhibition assay showed that this inhibitor remains with the possibility as anticancer agent.
IT 931426-94-7P 931426-95-8P 931426-96-9P
931426-97-0P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of cyclic tetrapeptides containing trifluoromethylketone as zinc binding functional group as potent anticancer agents)
RN 931426-94-7 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S)-2-amino-9,9,9-trifluoro-8-oxononanoyl] (CA INDEX NAME)

Absolute stereochemistry.



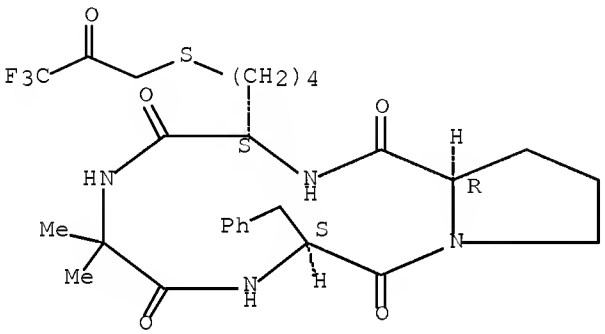
RN 931426-95-8 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-5-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norvalyl] (CA INDEX NAME)

Absolute stereochemistry.



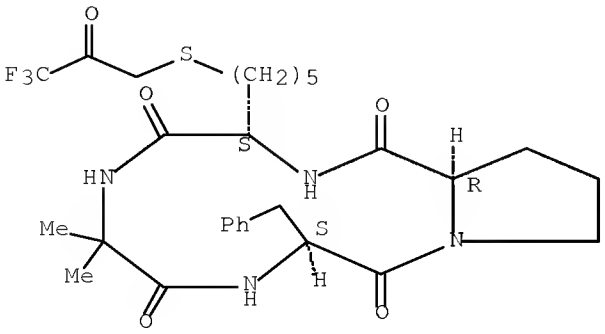
RN 931426-96-9 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-6-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norleucyl] (CA INDEX NAME)

Absolute stereochemistry.



RN 931426-97-0 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S)-2-amino-7-[(3,3,3-trifluoro-2-oxopropyl)thio]heptanoyl] (CA INDEX NAME)

Absolute stereochemistry.



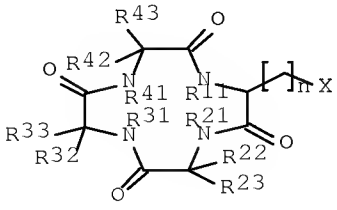
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:1156573 HCAPLUS Full-text
DOCUMENT NUMBER: 142:74844
TITLE: Preparation of cyclic tetrapeptide derivatives as histone deacetylase (HDAC) inhibitors and process for producing the same
INVENTOR(S): Yoshida, Minoru; Nishino, Norikazu
PATENT ASSIGNEE(S): Riken Corp., Japan
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113366	A1	20041229	WO 2004-JP8924	20040618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1640380	A1	20060329	EP 2004-746393	20040618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
US 20070185071	A1	20070809	US 2006-561298	20060607 <--
PRIORITY APPLN. INFO.:			JP 2003-177298 A	20030620
			WO 2004-JP8924 W	20040618

OTHER SOURCE(S): MARPAT 142:74844
GI



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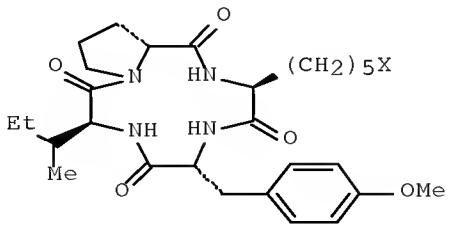


II

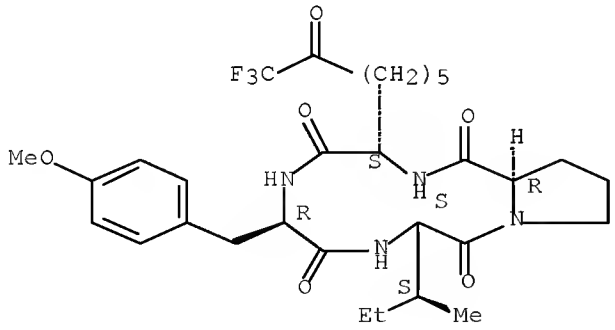
AB Cyclic tetrapeptide derivs. (I) [R11, R21, R31, R41 = H, Me; R22, R23, R33, R42, R43 = H, n-C1-6 alkyl, nonarom. cycloalkyl-n-C1-6 alkyl, (un)substituted aryl-n-C1-6 alkyl-n-C1-6 alkyl, nonarom. cycloalkyl, nonarom. cycloalkyl-nonarom. cycloalkyl, (un)substituted aryl-nonarom. cycloalkyl; or R21 and R22, R22 and R23, R31 and R32, R32 and R33, R41 and R42, or R42 and R43 together

form a noncyclic structure bonded through a direct bond or a cyclic structure bonded through a C1-5 n-alkylene, C1-5 n-alkylene having a C1-6 side chain, C1-5 n-alkylene having a C1-6 ring structure; n is selected within a range exhibiting HDAC activity; X = any structure capable of coordinating to the Zn atom located in the active center of histone deacetylase] are prepared These compds. are useful as HDAC inhibitors, tubulin deacetylase inhibitors, apoptosis inducers, differentiation inducers, neovascularization inhibitors, or cancer metastasis inhibitors. In particular, these compds. exhibit strong inhibitory activity against various subtype HDAC's and are useful for the treatment or prevention of HDAC 1, 4 and 6-related diseases such as cancer, autoimmune diseases, neurodegenerative diseases, skin diseases, or infection. There is further provided a process for producing the compound which is capable of readily synthesizing various types of compds. and is promising in the contribution to the development of HDAC inhibitor having novel properties. Cyclic tetrapeptides having a variety of zinc ligands (II) (X = 2-aminophenylaminocarbonyl, 2-hydroxyphenylaminocarbonyl, 2-aminophenoxycarbonyl, 2-mercaptophenylaminocarbonyl) inhibited HDAC 1 with IC50 of 4.04, 1.22, 0.40, and 2.03 μM, resp., HDAC 2 with IC50 of 15.7, 0.23, 0.24, and 0.23 μM, resp., and HDAC 6 with IC50 of 321, 5,042, 441, and 408 μM, resp.

IT 798553-32-9P 798553-33-0P 798553-34-1P
815581-29-4P 815581-31-8P 815581-32-9P
815581-33-0P 815581-34-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic tetrapeptide derivs. as histone deacetylase inhibitors for treating cancer, autoimmune diseases, neurodegenerative diseases, skin diseases, or infection)

RN 798553-32-9 HCAPLUS
CN Cyclo[(2S)-2-amino-9,9,9-trifluoro-8-oxononanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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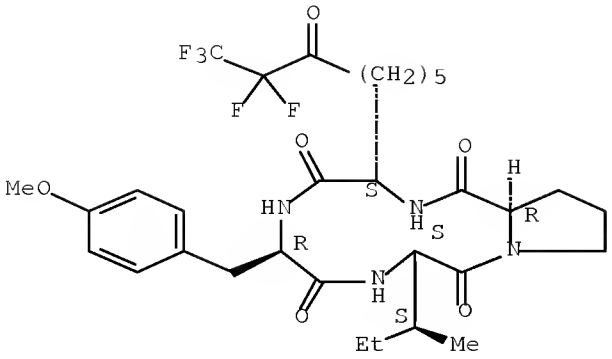
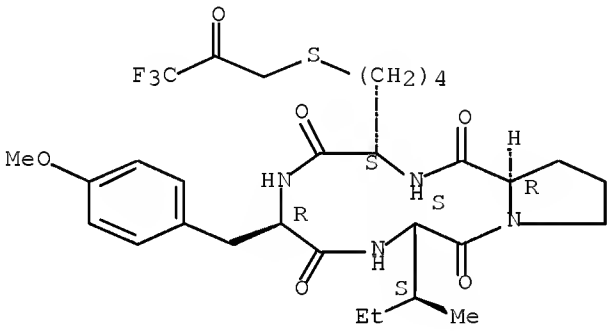
CN Cyclo[(2S)-2-amino-9,9,10,10,10-pentafluoro-8-oxodecanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



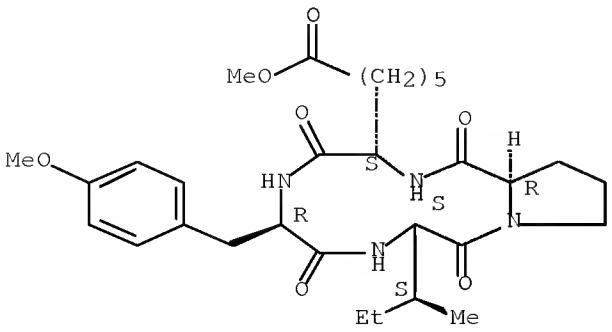
RN 798553-34-1 HCAPLUS
CN Cyclo[L-isoleucyl-D-prolyl-6-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norleucyl-O-methyl-D-tyrosyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



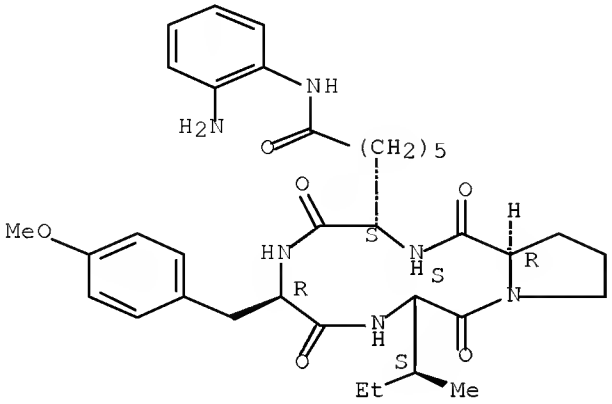
RN 815581-29-4 HCAPLUS
CN Cyclo[(2S)-2-amino-8-methoxy-8-oxooctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



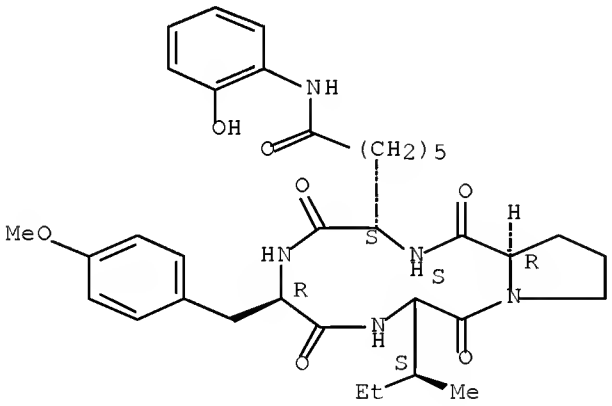
RN 815581-31-8 HCAPLUS
CN Cyclo[(2S)-2-amino-8-[(2-aminophenyl)amino]-8-oxooctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



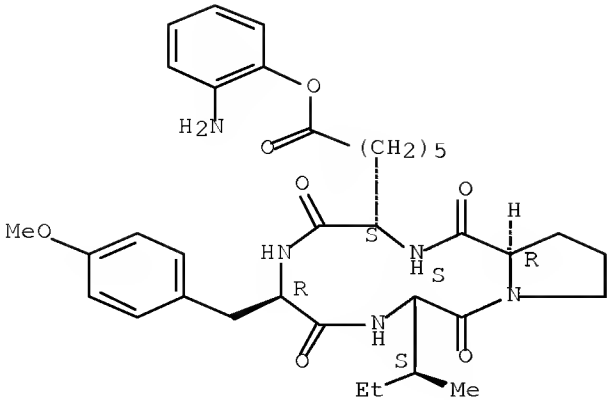
RN 815581-32-9 HCAPLUS
CN Cyclo[(2S)-2-amino-8-[(2-hydroxyphenyl)amino]-8-oxooctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



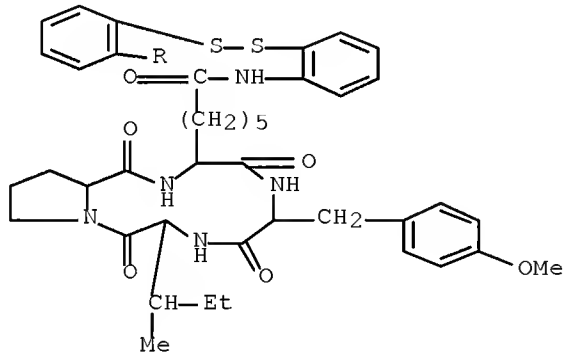
RN 815581-33-0 HCAPLUS
CN Cyclo[(2S)-2-amino-8-(2-aminophenoxy)-8-oxooctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.

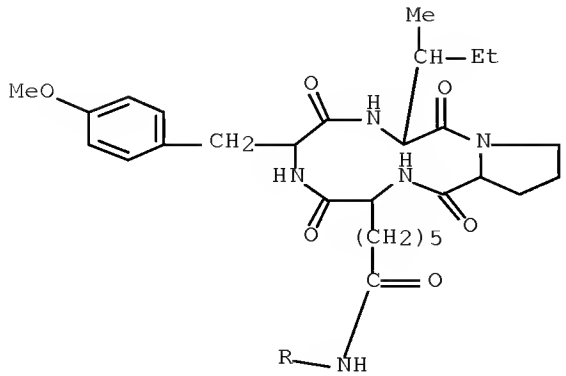


RN 815581-34-1 HCAPLUS
CN Cyclo[(2S)-2-amino-8-[(2-mercaptophenyl)amino]-8-oxooctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl], bimol. (1→1')-disulfide (9CI) (CA INDEX NAME)

PAGE 1-A

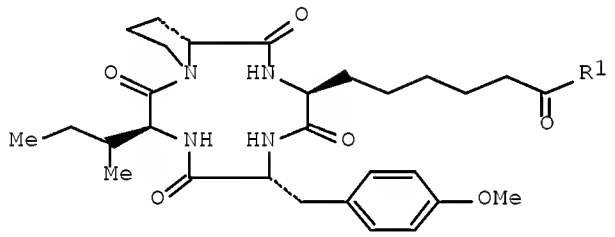


PAGE 2-A



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:791955 HCAPLUS Full-text
DOCUMENT NUMBER: 142:6802
TITLE: Novel histone deacetylase inhibitors: cyclic tetrapeptide with trifluoromethyl and pentafluoroethyl ketones
AUTHOR(S): Jose, Binoy; Oniki, Yusuke; Kato, Tamaki; Nishino, Norikazu; Sumida, Yuko; Yoshida, Minoru
CORPORATE SOURCE: CREST Research Project, Japan Science and Technology Agency, Saitama, 332-0012, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(21), 5343-5346
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:6802
GI



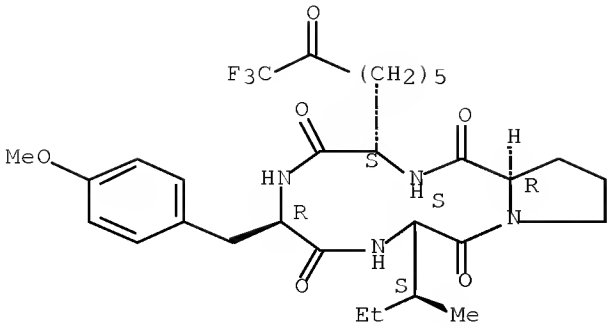
I

AB Cyclic tetrapeptides containing trifluoromethyl and pentafluoroethyl ketone as zinc binding functional group were synthesized as potent HDAC inhibitors. Thus, reacting cyclic tetrapeptide I (R1 = OCH2Ph) with LiOH/THF gave the lithium salt which was reacted with (F3CCO)2O or (F3CCF2CO)2O to give I (R1 = CF3, CF2CF3). Evaluation by human HDAC inhibition assay and p21 promoter assay showed that these inhibitors are promising anticancer agents.

IT 798553-32-9P 798553-33-0P 798553-34-1P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclic tetrapeptides with trifluoromethyl and pentafluoroethyl ketone groups, their histone deacetylase inhibitory activity, and anticancer activity)

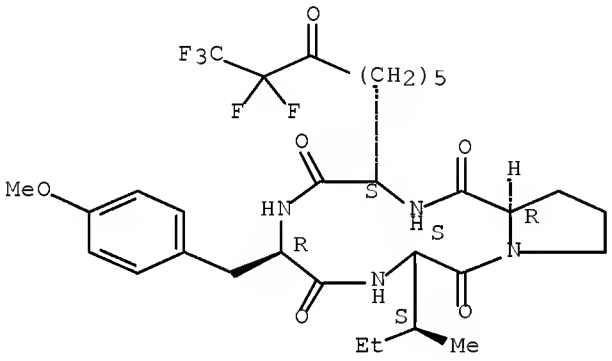
RN 798553-32-9 HCAPLUS
CN Cyclo[(2S)-2-amino-9,9,9-trifluoro-8-oxononanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



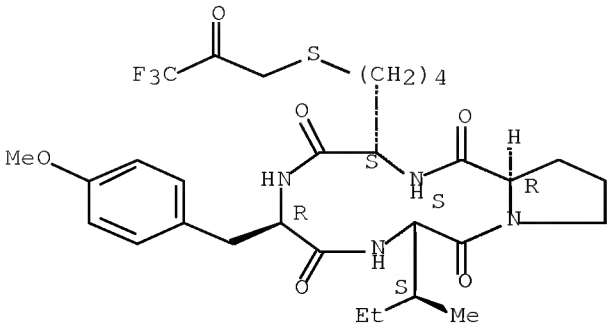
RN 798553-33-0 HCAPLUS
CN Cyclo[(2S)-2-amino-9,9,10,10,10-pentafluoro-8-oxodecanoyl-O-methyl-D-tyrosyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 798553-34-1 HCAPLUS
CN Cyclo[L-isoleucyl-D-prolyl-6-[(3,3,3-trifluoro-2-oxopropyl)thio]-L-norleucyl-O-methyl-D-tyrosyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

******* QUERY RESULTS *******
(COMPOUNDS OF CLAIM 2)

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     (FILE 'HCAPLUS' ENTERED AT 15:37:37 ON 04 FEB 2009)
L13          12 S L8 NOT L12

=> d que l13
L1               STR
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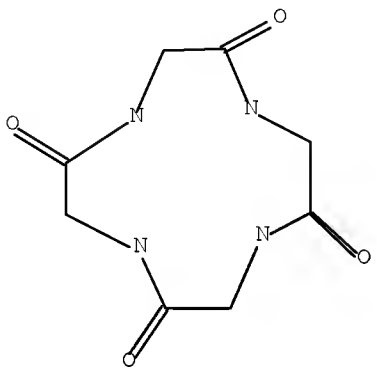
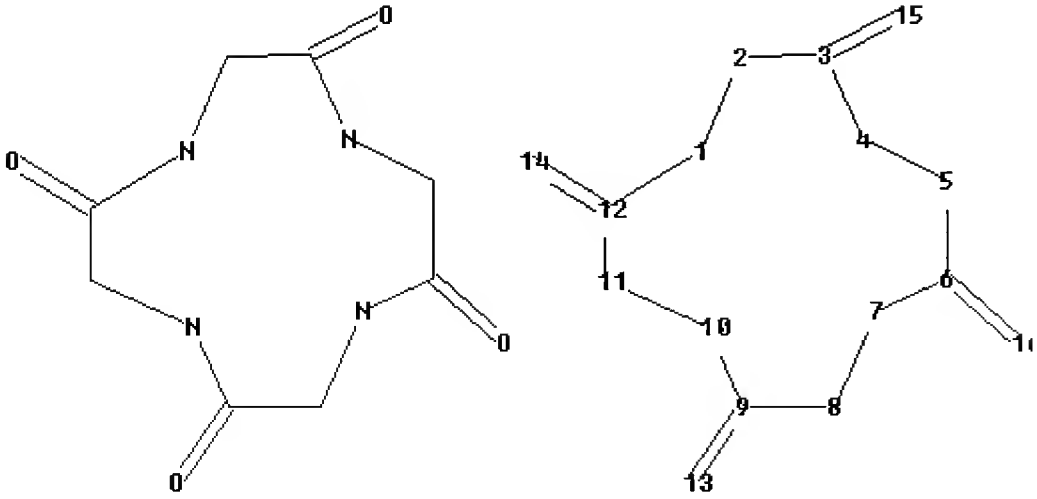


Structure attributes must be viewed using STN Express query preparation:

Uploading L2.str



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ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12
chain bonds :
3-15  6-16  9-13  12-14
ring bonds :
1-2  1-12  2-3  3-4  4-5  5-6  6-7  7-8  8-9  9-10  10-11  11-12
exact/norm bonds :
1-2  1-12  2-3  3-4  3-15  4-5  5-6  6-7  6-16  7-8  8-9  9-10  9-13  10-11  11-12
```

12-14

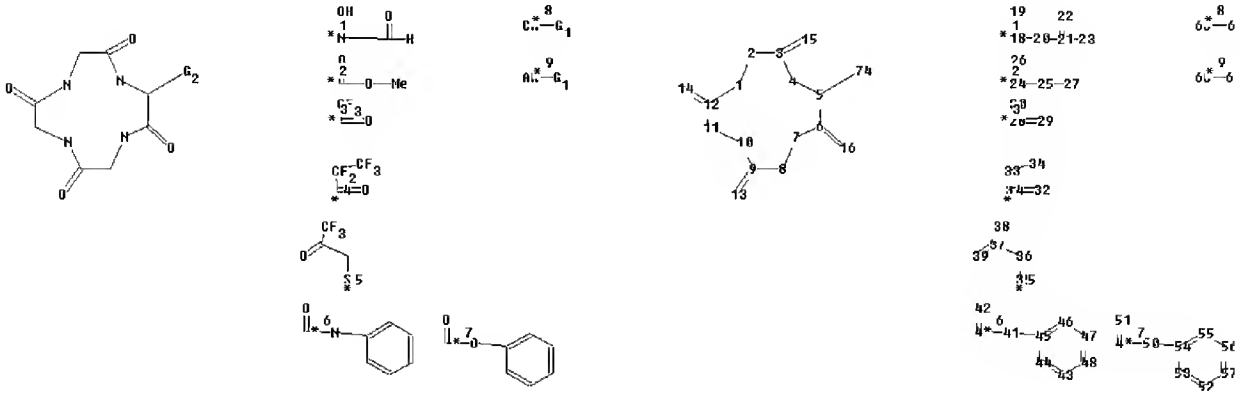
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 16:CLASS

L3 1852 SEA FILE=REGISTRY SSS FUL L1
L4 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation:

Uploading L4.str



chain nodes :
13 14 15 16 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
35 36 37 38 39 40 41 42 49 50 51 66 67 68 69 74
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 43 44 45 46 47 48 52 53 54 55 56
57
chain bonds :
3-15 5-74 6-16 9-13 12-14 18-19 18-20 20-21 21-22 21-23 24-25 24-26 25-
27
28-29 28-30 31-32 31-33 33-34 35-36 36-37 37-38 37-39 40-41 40-42 41-45
49-50 49-51
50-54 66-67 68-69
ring bonds :
1-2 1-12 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 43-44 43-48 44-
45
45-46 46-47 47-48 52-53 52-57 53-54 54-55 55-56 56-57
exact/norm bonds :
1-2 1-12 2-3 3-4 3-15 4-5 5-6 5-74 6-7 6-16 7-8 8-9 9-10 9-13 10-11
11-12 12-14 18-19 18-20 21-22 24-25 24-26 28-29 31-32 35-36 37-39 40-41
40-42 41-45
49-50 49-51 50-54 66-67 68-69
exact bonds :
20-21 21-23 25-27 28-30 31-33 33-34 36-37 37-38
normalized bonds :

43-44 43-48 44-45 45-46 46-47 47-48 52-53 52-57 53-54 54-55 55-56 56-57

isolated ring systems :
containing 43 : 52 :

G1:[*1],[*2],[*3],[*4],[*5],[*6],[*7]

G2:[*8],[*9]

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 16:CLASS 18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS
23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS
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L6 35 SEA FILE=REGISTRY SUB=L3 SSS FUL L4
L8 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L6
L9 1 SEA FILE=HCAPLUS ABB=ON PLU=ON US20070185071/PN
L10 14504 SEA FILE=HCAPLUS ABB=ON PLU=ON YOSHIDA M?/AU
L11 618 SEA FILE=HCAPLUS ABB=ON PLU=ON NISHINO N?/AU
L12 4 SEA FILE=HCAPLUS ABB=ON PLU=ON ((L10 OR L11) AND L8) OR (L8 AND L9)
L13 12 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 NOT L12

=> d l13 1-12 ibib abs hitstr hitind

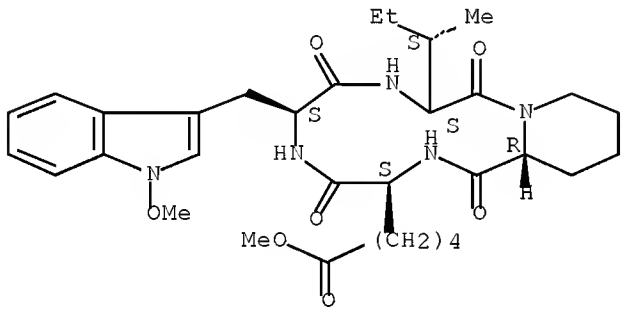
L13 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1477208 HCAPLUS Full-text
DOCUMENT NUMBER: 149:282442
TITLE: Pharmacophore modeling and virtual screening studies to design some potential histone deacetylase inhibitors as new leads
AUTHOR(S): Vadivelan, S.; Sinha, B. N.; Rambabu, G.; Boppana, Kiran; Jagarlapudi, Sarma A. R. P.
CORPORATE SOURCE: GVK Biosciences Pvt. Ltd., Hyderabad, 500037, India
SOURCE: Journal of Molecular Graphics & Modelling (2008), 26(6), 935-946
CODEN: JMGMFI; ISSN: 1093-3263
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Histone deacetylase is one of the important targets in the treatment of solid tumors and hematol. cancers. A total of 20 well-defined inhibitors were used to generate Pharmacophore models using and HypoGen module of Catalyst. These 20 mols. broadly represent 3 different chemotypes. The best HypoGen model consists of four-pharmacophore features, one hydrogen bond acceptor, one hydrophobic aliphatic and two ring aromatic centers. This model was validated

against 378 known HDAC inhibitors with a correlation of 0.897 as well as enrichment factor of 2.68 against a maximum value of 3. This model was further used to retrieve mols. from NCI database with 238,819 mols. A total of 4638 mols. from a pool of 238,819 mols. were identified as hits while 297 mols. were indicated as highly active. Also, a Similarity anal. has been carried out for set of 4638 hits with respect to most active mol. of each chemotypes which validated not only the Virtual Screening potential of the model but also identified the possible new Chemotypes. This type of Similarity anal. would prove to be efficient not only for lead generation but also for lead optimization.

IT 312957-00-9 1048351-90-1
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacophore modeling and virtual screening studies to design some potential histone deacetylase inhibitors as new leads)

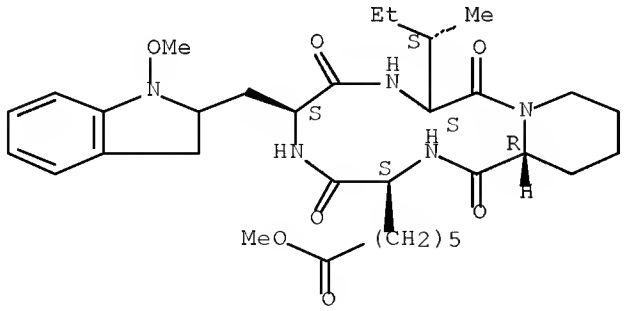
RN 312957-00-9 HCAPLUS
CN Cyclo[(2S)-2-amino-7-methoxy-7-oxoheptanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry.



RN 1048351-90-1 HCAPLUS
CN Cyclo[3-(2,3-dihydro-1-methoxy-1H-indol-2-yl)-L-alanyl-L-isoleucyl-(2R)-2-piperidinecarbonyl-(2S)-2-amino-8-methoxy-8-oxooctanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 1-3 (Pharmacology)
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RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacophore modeling and virtual screening studies to design some potential histone deacetylase inhibitors as new leads)

IT 593252-14-3 593252-15-4 593252-16-5 593252-17-6 593252-18-7
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1048357-31-8 1048357-44-3 1048670-10-5

RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacophore modeling and virtual screening studies to design some potential histone deacetylase inhibitors as new leads)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:2146 HCAPLUS Full-text
DOCUMENT NUMBER: 141:19501
TITLE: 3D-QSAR study on apicidin inhibit histone deacetylase
AUTHOR(S): Chen, Hai-feng; Kang, Jiu-hong; Li, Qiang; Zeng, Bao-shan; Yao, Xiao-jun; Fan, Bo-tao; Yuan, Shen-gang; Panay, A.; Doucet, J. P.
CORPORATE SOURCE: Key Laboratory of Computer Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, Peop. Rep. China
SOURCE: Chinese Journal of Chemistry (2003), 21(12), 1596-1607
CODEN: CJOCEV; ISSN: 1001-604X
PUBLISHER: Science Press
DOCUMENT TYPE: Journal
LANGUAGE: English

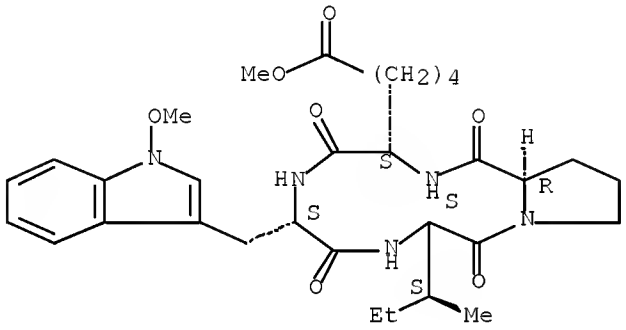
AB For Histone Deacetylase (HDAC) Inhibitor, four 3D-QSAR models for four types of different activities, were constructed. The cross-validated q2 value of CoMFA Model 1 is 0.624 and the noncross-validated r2 value is 0.939. The cross-validated q2 value of Model 2 for training set is 0.652 and the noncross-validated r2 value is 0.963. The cross-validated q2 value for Model 3 is 0.713, with noncross-validated r2 value 0.947. The cross-validated q2 value for Model 4 is 0.566 with noncross-validated r2 value 0.959. Their predicted abilities were validated by different test sets which did not include in training set. Then the relationship between substituents and activities was analyzed by using these models and the main influence elements in different positions (positions 8 and 14) were found. The polar donor

electron group of position 8 could increase the activity of inhibition of HDAC, because it could form chelation with the catalytic Zn. Suitable bulk and pos. groups at position 14 are favorable to anti-HDAC activity. These models could well interpret the relationship between inhibition activity and apicidin structure affording us important information for structure-based drug design.

IT 698364-48-6 698364-50-0 698364-52-2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(CoMFA and CoMSIA for construction of 3D-QSAR models of apicidin derivs. as histone deacetylase inhibitors)

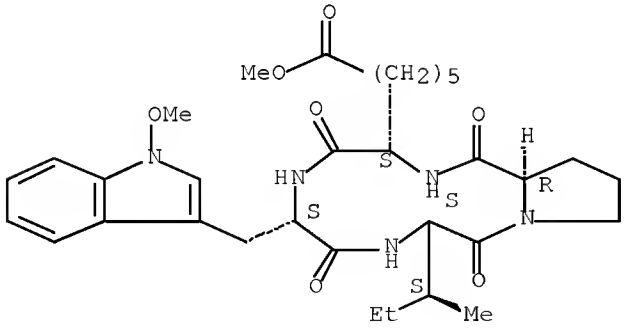
RN 698364-48-6 HCAPLUS
CN Cyclo[(2S)-2-amino-7-methoxy-7-oxoheptanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



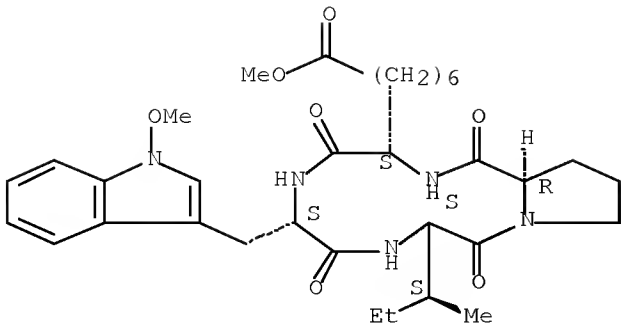
RN 698364-50-0 HCAPLUS
CN Cyclo[(2S)-2-amino-8-methoxy-8-oxooctanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 698364-52-2 HCAPLUS
CN Cyclo[(2S)-2-amino-9-methoxy-9-oxononanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 7-3 (Enzymes)
IT 9076-57-7, Histone Deacetylase 189337-29-9 366001-35-6 698364-38-4
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698364-50-0 698364-52-2 698364-54-4 698364-56-6
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698364-98-6 698364-99-7 698365-00-3 698365-01-4 698365-02-5
698365-03-6 698365-04-7
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(CoMFA and CoMSIA for construction of 3D-QSAR models of apicidin derivs. as histone deacetylase inhibitors)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:551539 HCAPLUS Full-text
DOCUMENT NUMBER: 139:117688
TITLE: Preparation of cyclic tetrapeptides as histone deacetylase inhibitors
INVENTOR(S): Satoh, Shigeki; Urano, Yasuharu; Osoda, Kazuhiko; Hosaka, Mitsuru; Sawada, Kozo; Inoue, Takayuki; Mori, Hiroaki; Takagaki, Shoji; Fujimura, Takao; Matsuoka, Hideaki; Yoshizawa, Katsuhiko
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan; et al.
SOURCE: PCT Int. Appl., 447 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057722	A2	20030717	WO 2002-JP13754	20021227
WO 2003057722	A3	20040422		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2471957	A1	20030717	CA 2002-2471957	20021227
AU 2002356443	A1	20030724	AU 2002-356443	20021227
EP 1458746	A2	20040922	EP 2002-806084	20021227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005517683	T	20050616	JP 2003-558036	20021227
US 20060229236	A1	20061012	US 2005-500113	20050208
PRIORITY APPLN. INFO.:			AU 2001-9779 A	20011228
			AU 2002-952117 A	20021010
			WO 2002-JP13754 W	20021227

OTHER SOURCE(S): MARPAT 139:117688
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

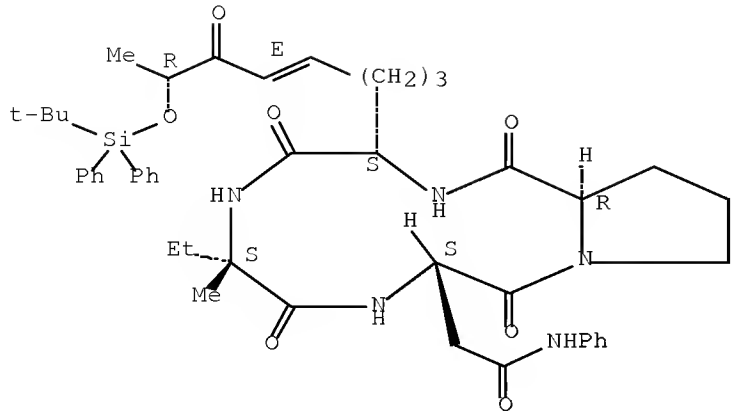
AB Cyclic tetrapeptides I [R1 is H; R2 is lower alkyl, aryl, (un)substituted arylalkyl, heterocyclylalkyl, cycloalkylalkyl, alkylcarbamoylalkyl, arylcarbamoylalkyl; R3, R4 are H, (un)substituted arylalkyl or heterocyclylalkyl, cycloalkylalkyl; or R3 and R4 are linked to form lower alkylene or a condensed ring or one of R3 and R4 is linked to the adjacent nitrogen atom to form a ring; R5 is H or alkyl; X is CH2 or CH2CH2; Z is alkylene or alkenylene; R6 is CR7R8R9 or NR7R8R9, where R7 is H, halo or optionally protected hydroxy, R8 is H, halo, alkyl or Ph, and R9 is H or alkyl] or their salts were prepared histone deacetylase inhibitors. Thus, compound II (Bn = benzyl) was prepared and shown to have IC50 < 100 nM and < 50 nM, resp., for inhibition of histone deacetylase and T-cell growth.

IT 561044-03-9P 561044-04-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of cyclic tetrapeptides as histone deacetylase inhibitors)

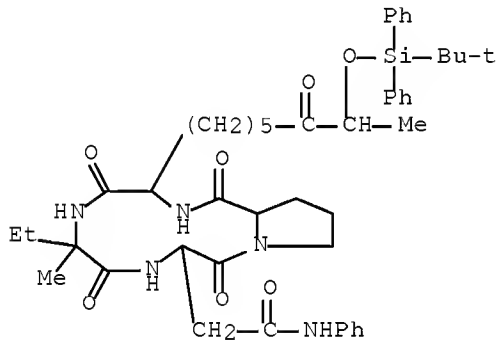
RN 561044-03-9 HCAPLUS

CN Cyclo[N-phenyl-L-asparaginyl-D-prolyl-(2S,6E,9R)-2-amino-9-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-8-oxo-6-decenoyl-L-isovalyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

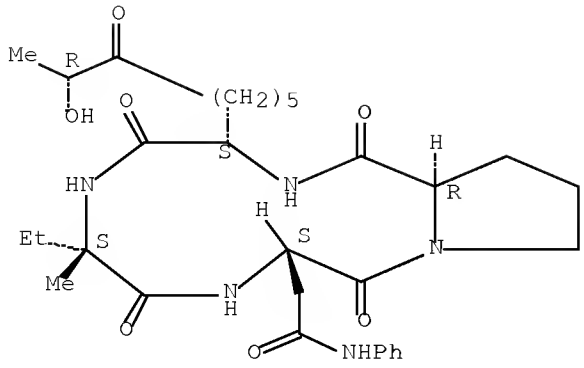


RN 561044-04-0 HCAPLUS
CN Cyclo[N-phenyl-L-asparaginyl-D-prolyl-(2S,9R)-2-amino-9-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-8-oxodecanoyl-L-isovalyl] (9CI) (CA INDEX NAME)



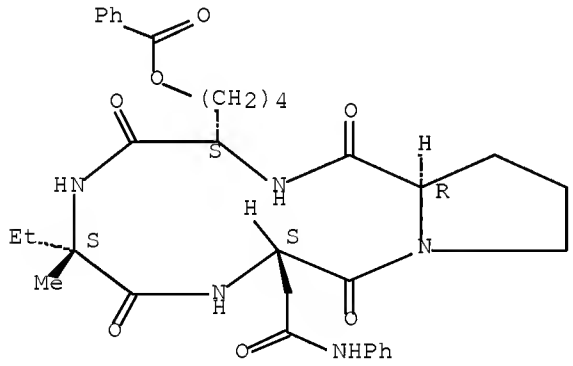
IT 561044-05-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic tetrapeptides as histone deacetylase inhibitors)
RN 561044-05-1 HCAPLUS
CN Cyclo[N-phenyl-L-asparaginyl-D-prolyl-(2S,9R)-2-amino-9-hydroxy-8-oxodecanoyl-L-isovalyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



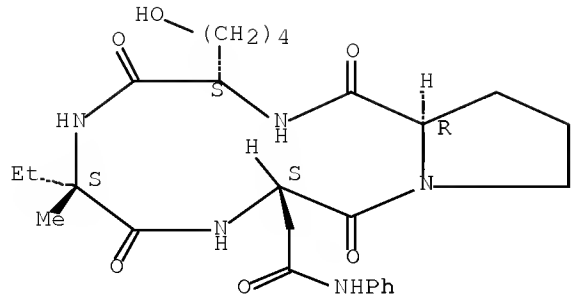
IT 561039-85-8P 561039-86-9P 561039-87-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclic tetrapeptides as histone deacetylase inhibitors)
RN 561039-85-8 HCAPLUS
CN Cyclo[N-phenyl-L-asparaginyl-D-prolyl-6-(benzoyloxy)-L-norleucyl-L-isovalyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



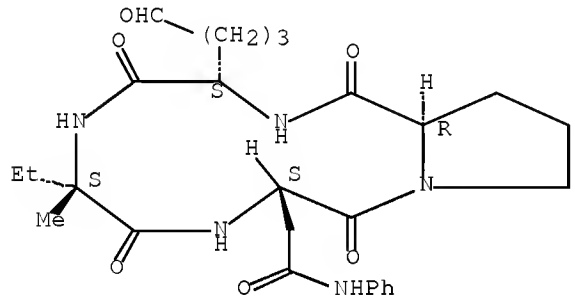
RN 561039-86-9 HCAPLUS
CN Cyclo(N-phenyl-L-asparaginyl-D-prolyl-6-hydroxy-L-norleucyl-L-isovalyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 561039-87-0 HCAPLUS
CN Cyclo(N-phenyl-L-asparaginyl-D-prolyl-6-oxo-L-norleucyl-L-isovalyl) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IC ICM C07K005-12
ICS A61K038-12; A61P029-00; A61P035-00; A61P037-06
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63
IT 264259-89-4P 561038-04-8P 561042-32-8P 561042-33-9P 561042-34-0P
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561045-51-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of cyclic tetrapeptides as histone deacetylase inhibitors)

IT 264259-90-7P 561042-37-3P 561042-38-4P 561042-39-5P 561042-44-2P
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561045-53-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic tetrapeptides as histone deacetylase inhibitors)

IT 561039-19-8P 561039-20-1P 561039-21-2P 561039-22-3P 561039-23-4P
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561041-65-4P 561041-66-5P 561041-67-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

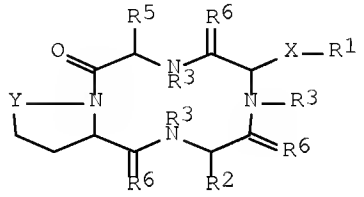
(preparation of cyclic tetrapeptides as histone deacetylase inhibitors)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:319478 HCAPLUS Full-text
DOCUMENT NUMBER: 138:287984
TITLE: Preparation of apicidin-derived cyclic tetrapeptides
INVENTOR(S): Meinke, Peter T.; Schmatz, Dennis; Myers, Robert W.; Rattray, Sandra J.; Colletti, Steven L.; Wyvratt, Matthew J.; Fisher, Michael H.; Gurnett, Anne M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 104 pp., Cont.-in-part of U.S. Ser. No. 614,793.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20030078369	A1	20030424	US 2002-66451	20020131
PRIORITY APPLN. INFO.:			US 1999-145329P	P 19990723
			US 2000-614793	A2 20000712

OTHER SOURCE(S): MARPAT 138:287984
GI



I

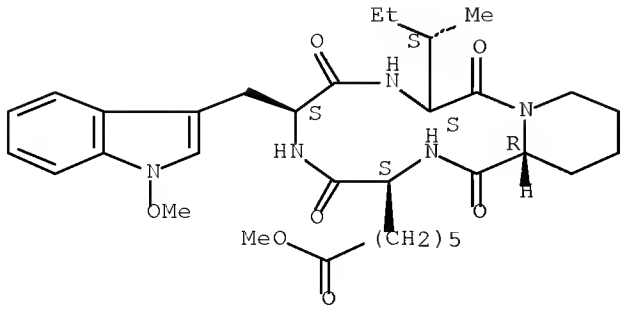
AB Cyclic tetrapeptide compds. I [X = CH2, CO, CHOH, alkoxy- or aryloxymethylene, etc., :CH, or not present; Y = (CH2)n, where n = 1 or 2; R1 = H, alkyl, aryl, acyl, CN, CO2H or ester, carboxamido, etc.; R2 = (un)substituted alkyl, alkenyl, or alkynyl, alkoxy, alkoxyalkyl; R3 = H, halo, OH, alkoxy, aryloxy, etc., alkyl, aryl; R5 = iso-Pr, sec-butyl; R6 = O, S, H2 (with provisos)] derived from apicidin were prepared for therapeutic inhibition of histone deacetylase activity. Thus, treating 300 mg apicidin with 18 mg NaBH4 in MeOH and stirring 4 h at room temperature afforded carbonyl reduction product cyclo(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2- amino-8-hydroxydecanoyl) (pip = pipecolic acid residue).

IT 312956-79-9P 312957-02-1P 315189-85-6P
315189-91-4P 322000-83-9P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of apicidin-derived cyclic tetrapeptides)

RN 312956-79-9 HCAPLUS

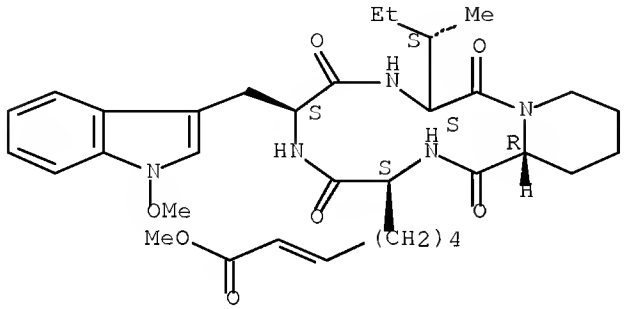
CN Cyclo[(2S)-2-amino-8-methoxy-8-oxooctanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



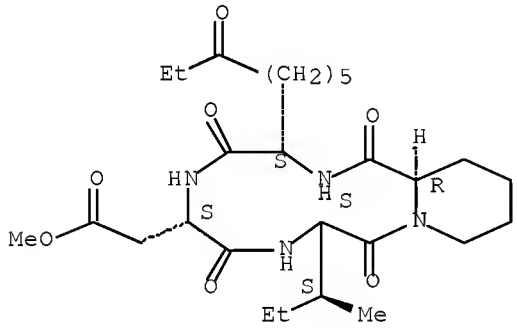
RN 312957-02-1 HCAPLUS
CN Cyclo[(2S)-2-amino-9-methoxy-9-oxo-7-nonenoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



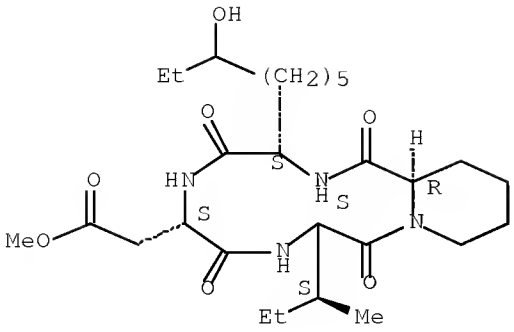
RN 315189-85-6 HCAPLUS
CN Cyclo[(2S)-2-amino-8-oxodecanoyl-L-α-aspartyl-L-isoleucyl-(2R)-2-piperidinecarbonyl], methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



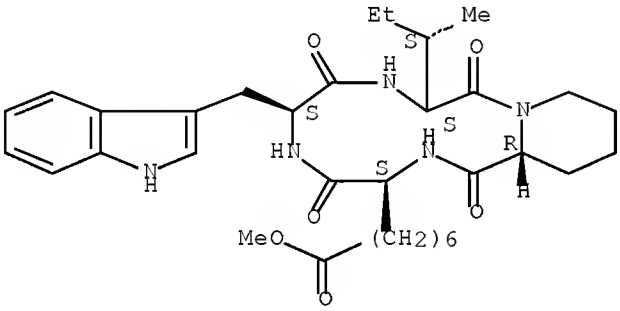
RN 315189-91-4 HCAPLUS
CN Cyclo[(2S)-2-amino-8-hydroxydecanoyl-L-α-aspartyl-L-isoleucyl-(2R)-2-piperidinecarbonyl], methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



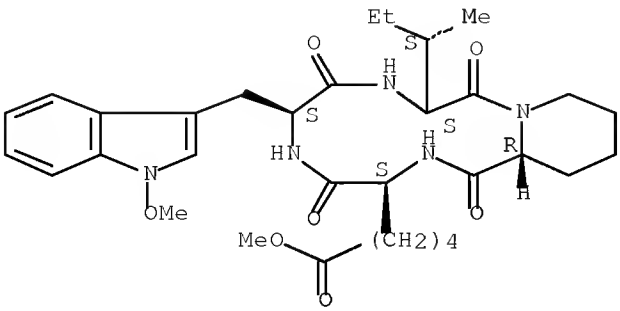
RN 322000-83-9 HCAPLUS
CN Cyclo[(2S)-2-amino-9-methoxy-9-oxononanoyl-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 312957-00-9P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of apicidin-derived cyclic tetrapeptides)
RN 312957-00-9 HCAPLUS
CN Cyclo[(2S)-2-amino-7-methoxy-7-oxoheptanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry.



IC ICM C07K007-54
ICS C07D245-00
INCL 530317000; 540460000
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7
IT 183506-67-4P 189127-20-6P 189337-31-3P 312956-77-7P 312956-78-8P
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RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent);
USES (Uses)
(preparation of apicidin-derived cyclic tetrapeptides)
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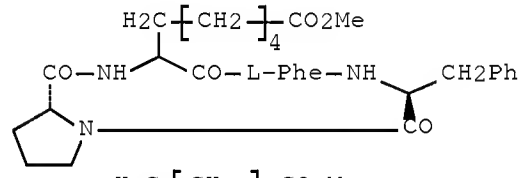
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
study); PREP (Preparation); USES (Uses)

(preparation of apicidin-derived cyclic tetrapeptides)

L13 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:954421 HCAPLUS Full-text
DOCUMENT NUMBER: 138:170518
TITLE: Conformationally Homogeneous Cyclic Tetrapeptides: Useful New Three-Dimensional Scaffolds
AUTHOR(S): Glenn, Matthew P.; Kelso, Michael J.; Tyndall, Joel D. A.; Fairlie, David P.
CORPORATE SOURCE: Centre for Drug Design and Development Institute for Molecular Bioscience, University of Queensland, Brisbane, 4072, Australia
SOURCE: Journal of the American Chemical Society (2003), 125(3), 640-641
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:170518
GI



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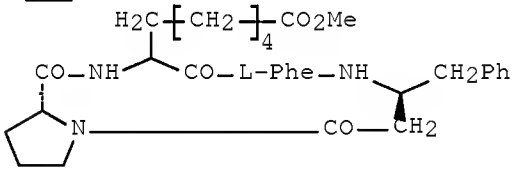
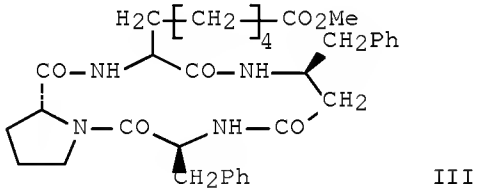


II



III

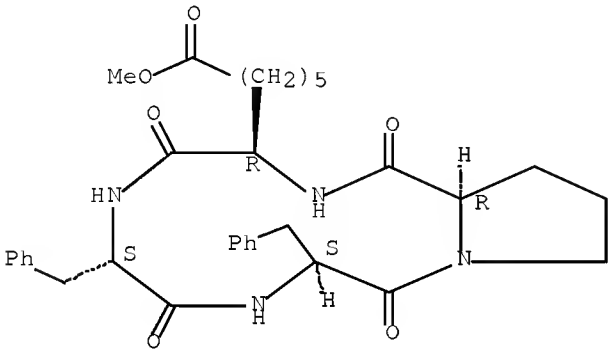
AB The authors demonstrate that certain cyclic tetrapeptides (13-membered ring with a β-amino acid) are easier to synthesize, chemical more stable, conformationally homogeneous and are novel three-dimensional scaffolds. To this purpose, cyclic tetrapeptides I-III [both diastereomers arising from (R)- and (S)-2-aminosuberic acids were obtained] were synthesized and their conformations were studied. Appropriate placement of a β-amino acid in a tetrapeptide, such as β-homophenylalanine in III, created a 13-membered ring that was shown to be easier to cyclize, hydrolytically more stable, and conformationally homogeneous in polar solvents such as DMSO and water. Three-dimensional structures revealed that I-III are novel rigid scaffolds, their

unique side-chain projections matching a structurally diverse range of useful nonpeptidic templates that are found in natural products.

IT 496875-96-8P 496875-98-0P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclic tetrapeptides with and without β-amino acids to determine the effects of β-amino acids on cyclization, hydrolytic susceptibility and on conformations of the peptides)

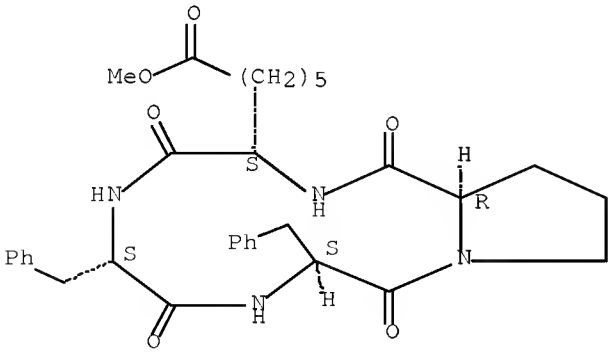
RN 496875-96-8 HCAPLUS
CN Cyclo[(2R)-2-amino-8-methoxy-8-oxooctanoyl-L-phenylalanyl-L-phenylalanyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 496875-98-0 HCAPLUS
CN Cyclo[(2S)-2-amino-8-methoxy-8-oxooctanoyl-L-phenylalanyl-L-phenylalanyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



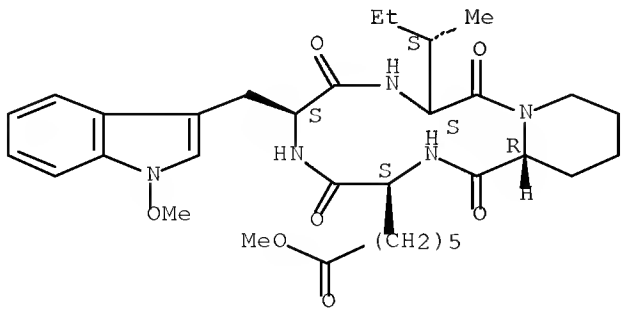
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 22

IT 496875-96-8P 496875-98-0P 496876-04-1P 496876-05-2P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclic tetrapeptides with and without β-amino acids to

determine the effects of β-amino acids on cyclization, hydrolytic susceptibility and on conformations of the peptides)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

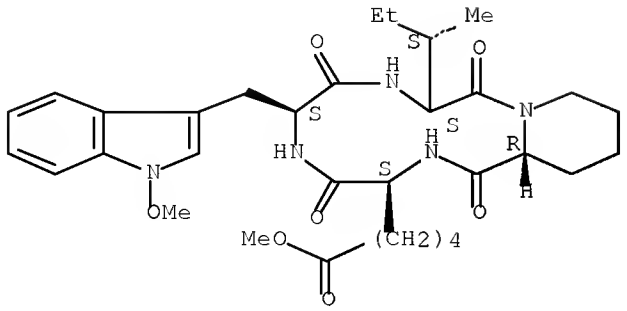
L13 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:83649 HCAPLUS Full-text
DOCUMENT NUMBER: 134:289954
TITLE: Broad spectrum antiprotozoal agents that inhibit histone deacetylase: structure-activity relationships of apicidin. Part 1
AUTHOR(S): Colletti, S. L.; Myers, R. W.; Darkin-Rattray, S. J.; Gurnett, A. M.; Dulski, P. M.; Galuska, S.; Allocco, J. J.; Ayer, M. B.; Li, C.; Lim, J.; Crumley, T. M.; Cannova, C.; Schmatz, D. M.; Wyvratt, M. J.; Fisher, M. H.; Meinke, P. T.
CORPORATE SOURCE: Merck Research Laboratories, Merck & Co., Inc., Rahway, NJ, 07065, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(2), 107-111
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Apicidin, a natural product recently isolated at Merck, inhibits both mammalian and protozoan histone deacetylases (HDACs). The conversion of apicidin, a nanomolar inhibitor of HDACs, into a series of side-chain analogs that display picomolar enzyme affinity is described within this structure-activity study.
IT 312956-79-9 312957-00-9 312957-03-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiprotozoal activity and histone deacetylase inhibition by apicidin analogs)
RN 312956-79-9 HCAPLUS
CN Cyclo[(2S)-2-amino-8-methoxy-8-oxooctanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



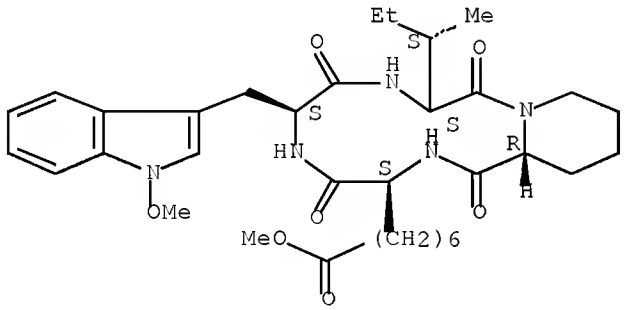
RN 312957-00-9 HCAPLUS
CN Cyclo[(2S)-2-amino-7-methoxy-7-oxoheptanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry.



RN 312957-03-2 HCAPLUS
CN Cyclo[(2S)-2-amino-9-methoxy-9-oxononanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



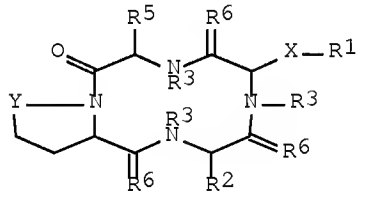
CC 1-3 (Pharmacology)
Section cross-reference(s): 7, 10, 26, 27
IT 312956-79-9 312956-84-6 312956-86-8 312956-88-0
312956-89-1 312956-90-4 312956-91-5 312956-92-6 312956-95-9
312956-96-0 312957-00-9 312957-01-0 312957-03-2
312957-04-3 314058-18-9 314058-19-0 314058-20-3 314058-23-6
314058-24-7 314058-25-8 314058-27-0 322000-77-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiprotozoal activity and histone deacetylase inhibition by apicidin analogs)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:78233 HCAPLUS Full-text
DOCUMENT NUMBER: 134:131817
TITLE: Preparation of apicidin-derived cyclic tetrapeptides
INVENTOR(S): Meinke, Peter T.; Schmatz, Dennis; Fisher, Michael H.; Rattray, Sandra J.; Colletti, Steven L.; Wyvratt, Matthew J.; Myers, Robert W.; Gurnett, Anne M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 229 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007042	A1	20010201	WO 2000-US19627	20000719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2378849	A1	20010201	CA 2000-2378849	20000719
EP 1204411	A1	20020515	EP 2000-947507	20000719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003505417	T	20030212	JP 2001-511926	20000719
PRIORITY APPLN. INFO.:			US 1999-145329P P	19990723
			WO 2000-US19627 W	20000719

OTHER SOURCE(S): MARPAT 134:131817
GI



I

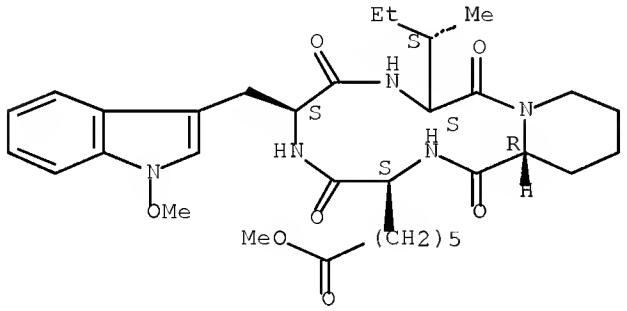
AB Cyclic tetrapeptide compds. I [X = CH2, CO, CHOH, alkoxy- or aryloxymethylene, etc., :CH, or not present; Y = (CH2)n, where n = 1 or 2; R1 = H, alkyl, aryl, acyl, CN, CO2H or ester, carboxamido, etc.; R2 = (un)substituted alkyl, alkenyl, or alkynyl, (CH2)nii-O-(CH2)mii, where nii, mii = 0-7; R3 = H, halo, OH, alkoxy, aryloxy, etc., alkyl, aryl; R5 = iso-Pr, sec-butyl; R6 = O, S, H2 (with provisos)] derived from apicidin were prepared for therapeutic inhibition of histone deacetylase activity. Thus, treating 300 mg apicidin with 18 mg NaBH4 in MeOH and stirring 4 h at room temperature afforded carbonyl reduction product cyclo(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-hydroxydecanoyl) (pip = pipecolic acid residue).

IT 312956-79-9P 312957-02-1P 315189-85-6P
315189-91-4P 322000-83-9P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of apicidin-derived cyclic tetrapeptides)

RN 312956-79-9 HCAPLUS

CN Cyclo[(2S)-2-amino-8-methoxy-8-oxooctanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

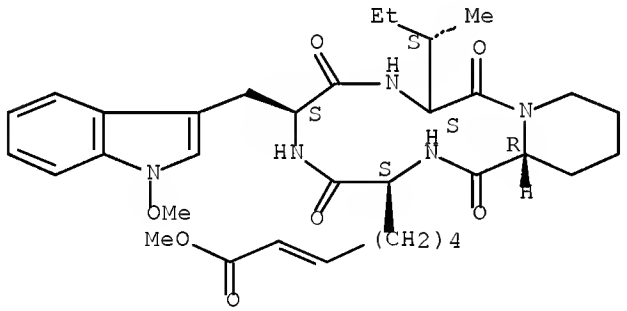
Absolute stereochemistry.



RN 312957-02-1 HCAPLUS

CN Cyclo[(2S)-2-amino-9-methoxy-9-oxo-7-nonenoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

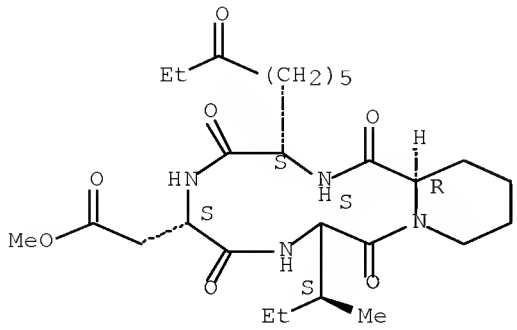
Absolute stereochemistry.
Double bond geometry unknown.



RN 315189-85-6 HCAPLUS

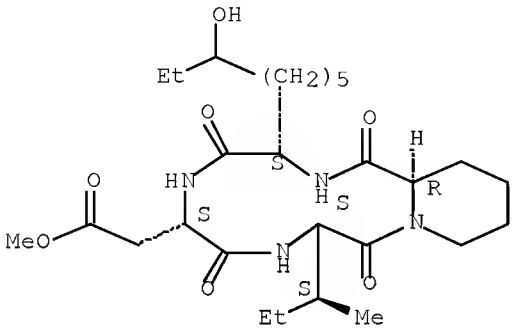
CN Cyclo[(2S)-2-amino-8-oxodecanoyl-L-α-aspartyl-L-isoleucyl-(2R)-2-piperidinecarbonyl], methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



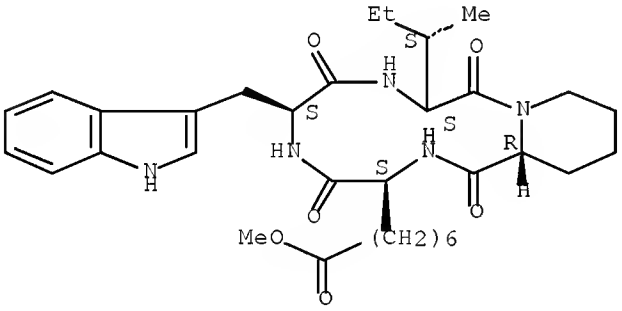
RN 315189-91-4 HCAPLUS
CN Cyclo[(2S)-2-amino-8-hydroxydecanoyl-L-α-aspartyl-L-isoleucyl-(2R)-2-piperidinecarbonyl], methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



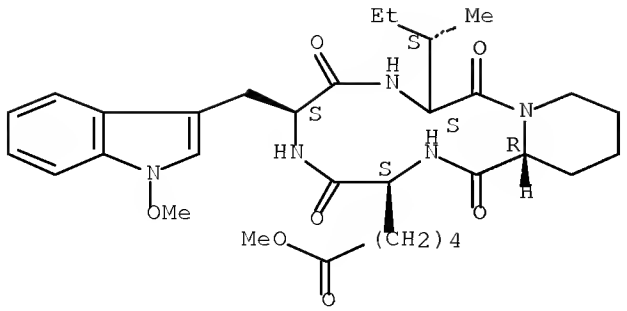
RN 322000-83-9 HCAPLUS
CN Cyclo[(2S)-2-amino-9-methoxy-9-oxononanoyl-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 312957-00-9P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of apicidin-derived cyclic tetrapeptides)
RN 312957-00-9 HCAPLUS
CN Cyclo[(2S)-2-amino-7-methoxy-7-oxoheptanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry.



IC ICM A61K031-395
ICS A61K038-12; C07D257-10; C07K005-12

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7

IT 183506-67-4P 189127-20-6P 189337-31-3P 312956-77-7P 312956-78-8P
312956-79-9P 312956-87-9P 312956-89-1P 312956-93-7P
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RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent);
USES (Uses)
(preparation of apicidin-derived cyclic tetrapeptides)

IT 189337-30-2P 189337-32-4P 312956-80-2P 312956-81-3P 312956-82-4P
312956-83-5P 312956-86-8P 312956-88-0P 312956-90-4P 312956-91-5P
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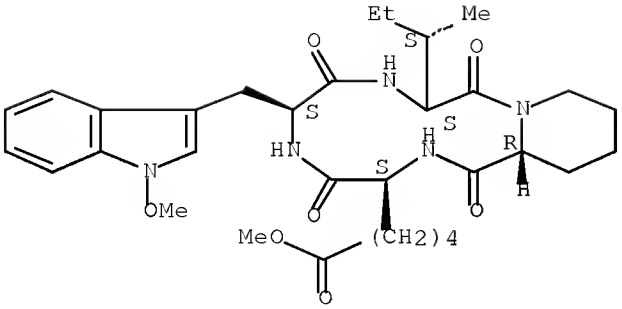
322002-16-4P 322002-17-5P 322002-18-6P 322411-12-1P 322411-13-2P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of apicidin-derived cyclic tetrapeptides)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

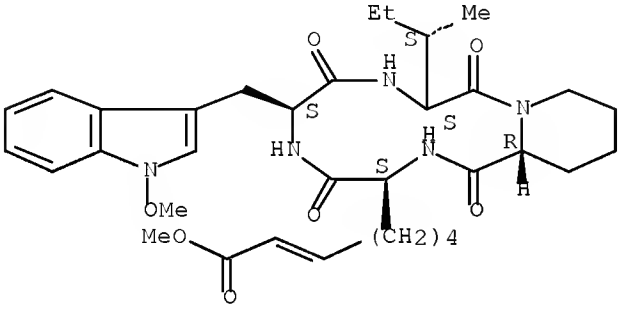
L13 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:805814 HCAPLUS Full-text
DOCUMENT NUMBER: 134:42434
TITLE: Synthesis of side chain modified apicidin derivatives: potent mechanism-based histone deacetylase inhibitors
AUTHOR(S): Meinke, Peter T.; Colletti, Steven L.; Ayer, Michelle B.; Darkin-Rattray, Sandra J.; Myers, Robert W.; Schmatz, Dennis M.; Wyvratt, Matthew J.; Fisher, Michael H.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, Merck and Co., Inc., Rahway, NJ, 07065, USA
SOURCE: Tetrahedron Letters (2000), 41(41), 7831-7835
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:42434
AB An efficient degradation of apicidin's ketone-containing side chain to two common intermediates (the C7-aldehyde and the C8-Me ester) is described. From these intermediates, a series of potent mechanism-based histone deacetylase inhibitors was prepared to facilitate biochem. studies.
IT 312957-00-9P 312957-02-1P 312957-03-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of side chain modified apicidin derivs. for use as histone deacetylase inhibitors)
RN 312957-00-9 HCAPLUS
CN Cyclo[(2S)-2-amino-7-methoxy-7-oxoheptanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry.



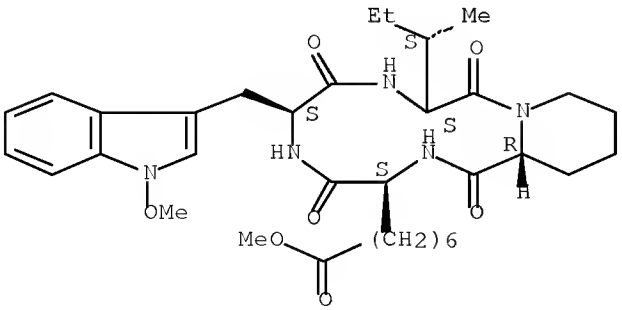
RN 312957-02-1 HCAPLUS
CN Cyclo[(2S)-2-amino-9-methoxy-9-oxo-7-nonenoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 312957-03-2 HCAPLUS
CN Cyclo[(2S)-2-amino-9-methoxy-9-oxononanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

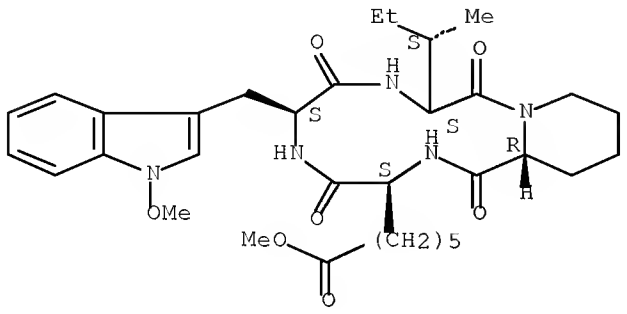
Absolute stereochemistry.



IT 312956-79-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of side chain modified apicidin derivs. for use as histone

deacetylase inhibitors)
RN 312956-79-9 HCAPLUS
CN Cyclo[(2S)-2-amino-8-methoxy-8-oxooctanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
IT 189337-30-2P 312956-77-7P 312956-78-8P 312956-80-2P 312956-84-6P
312956-87-9P 312956-93-7P 312956-94-8P 312956-96-0P 312956-98-2P
312957-00-9P 312957-02-1P 312957-03-2P
312957-05-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of side chain modified apicidin derivs. for use as histone deacetylase inhibitors)
IT 312956-79-9P 312956-81-3P 312956-82-4P 312956-83-5P
312956-85-7P 312956-86-8P 312956-88-0P 312956-89-1P 312956-90-4P
312956-91-5P 312956-92-6P 312956-95-9P 312956-97-1P 312956-99-3P
312957-01-0P 312957-04-3P 312957-06-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of side chain modified apicidin derivs. for use as histone deacetylase inhibitors)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

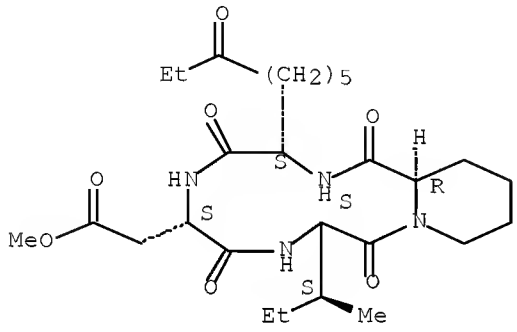
L13 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:805813 HCAPLUS Full-text
DOCUMENT NUMBER: 134:71889
TITLE: Tryptophan-replacement and indole-modified apicidins: synthesis of potent and selective antiprotozoal agents
AUTHOR(S): Colletti, Steven L.; Li, Chunshi; Fisher, Michael H.; Wyvratt, Matthew J.; Meinke, Peter T.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, Merck and Co., Inc., Rahway, NJ, 07065, USA
SOURCE: Tetrahedron Letters (2000), 41(41), 7825-7829
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A ruthenium tetraoxide catalyzed degradation of apicidin's tryptophan indole provided access to two useful carboxylic acid homolog intermediates. The synthesis of a series of potent and/or selective ketone homologs and 2-arylindoles derived from apicidin is described.

IT 315189-85-6P 315189-91-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tryptophan-replacement and indole-modified apicidins as antiprotozoal agents)

RN 315189-85-6 HCAPLUS

CN Cyclo[(2S)-2-amino-8-oxodecanoyl-L-α-aspartyl-L-isoleucyl-(2R)-2-piperidinecarbonyl], methyl ester (9CI) (CA INDEX NAME)

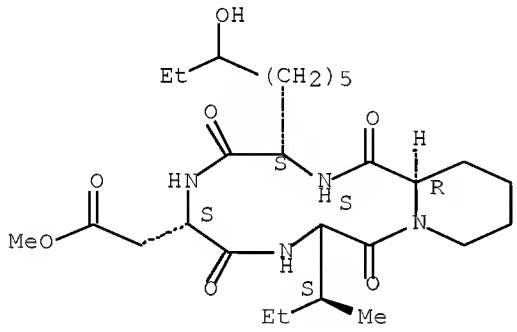
Absolute stereochemistry.



RN 315189-91-4 HCAPLUS

CN Cyclo[(2S)-2-amino-8-hydroxydecanoyl-L-α-aspartyl-L-isoleucyl-(2R)-2-piperidinecarbonyl], methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

IT 183506-67-4P 189127-20-6P 315189-85-6P 315189-86-7P
315189-87-8P 315189-88-9P 315189-91-4P 315189-92-5P
315189-98-1P 315189-99-2P 315190-08-0P 315190-09-1P 315190-10-4P
315190-11-5P 315190-12-6P 315190-13-7P 315190-14-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tryptophan-replacement and indole-modified apicidins as antiprotozoal agents)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS

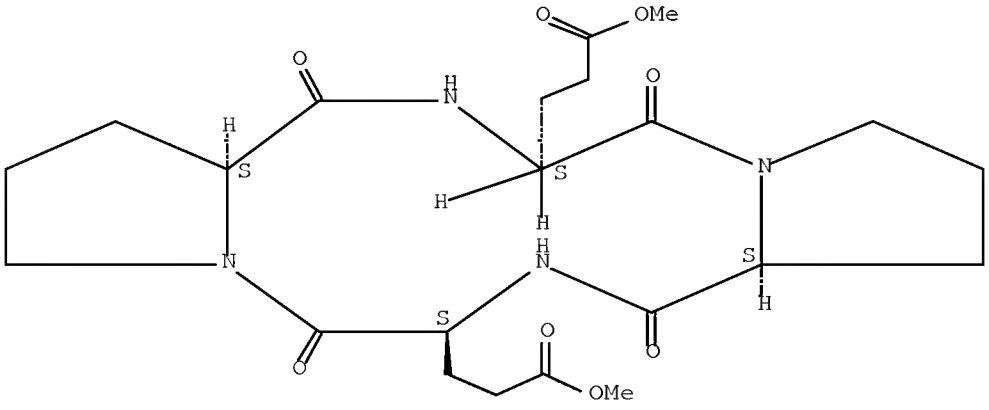
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1990:134663 HCAPLUS Full-text
DOCUMENT NUMBER: 112:134663
ORIGINAL REFERENCE NO.: 112:22657a,22660a
TITLE: Synthesis and interaction with metal ions of cyclic oligopeptides bearing carboxyl groups
AUTHOR(S): Fusaoka, Yosinari; Ozeki, Eiichi; Kimura, Shunsaku; Imanishi, Yukio
CORPORATE SOURCE: Dep. Polym. Chem., Kyoto Univ., Kyoto, 606, Japan
SOURCE: International Journal of Peptide & Protein Research (1989), 34(2), 104-10
CODEN: IJPPC3; ISSN: 0367-8377
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclic di- and tetrapeptides bearing carboxyl or carboxylate groups, cyclo[Glu(OBzl)-Glu(OMe)], cyclo[Glu-Glu(OMe)], cyclo(Glu-Glu), cyclo[Glu(OMe)-Pro)2, and cyclo(Glu-Pro)2, were synthesized and investigated on the intramol. interaction of carboxyl side chains in the complexation with metal ions in relation with the conformation. The 3 kinds of cyclic dipeptides took a flagpole boat conformation. Folded conformation of side chains was predominant for cyclo[Glu(OBzl)-Glu(OMel)] and cyclo[Glu-Glu(OMe)]. However, cyclo(Glu-Glu) took an unfolded conformation. Intramol. interaction of carboxyl groups was observed neither in free state nor in complexation with metal ions. The intramol. interaction of carboxyl groups was observed in the case of cyclo(Glu-Pro)2 in the absence of metal ions added. Cyclo[Glu(OMe)-Pro]2 and cyclo(Glu-Pro)2 formed a complex with Ca2+ and Ba2+ without participation of side chains.

IT 82067-64-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and saponification and conformation of and metal ion complexation by)
RN 82067-64-9 HCAPLUS
CN Cyclo(L-α-glutamyl-L-prolyl-L-α-glutamyl-L-prolyl), dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 6-3 (General Biochemistry)
Section cross-reference(s): 34
IT 82067-64-9P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and saponification and conformation of and metal ion complexation by)

L13 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1983:558832 HCAPLUS Full-text
DOCUMENT NUMBER: 99:158832
ORIGINAL REFERENCE NO.: 99:24372h,24373a
TITLE: Electron transport by transition-metal-ion complex of cyclic peptide having polar substituents
AUTHOR(S): Imanishi, Yukio
CORPORATE SOURCE: Dep. Polymer Chem., Kyoto Univ., Kyoto, Japan
SOURCE: Kenkyu Hokoku - Asahi Garasu Kogyo Gijutsu Shoreikai (1982), 41, 279-87
CODEN: AGKGAA; ISSN: 0365-2599
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

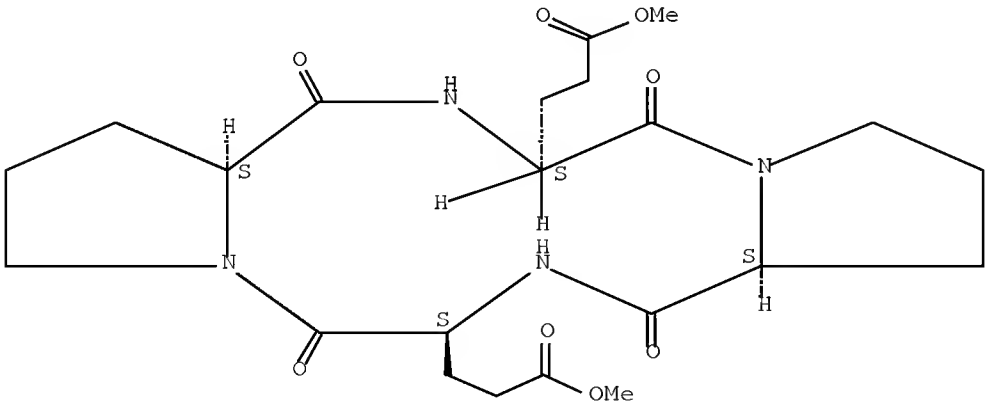
AB Cyclo(Glu-Glu), cyclo[Glu(OMe)-Glu], cyclo[Glu(OMe)-Glu(OCH2Ph)], cyclo(Glu-Pro)2 (I), cyclo[Glu(OMe)-Pro]2 (II), cyclo(Lys-Pro)4, cyclo(Phe-Pro)4, cyclo(Leu-Pro)4 (III), and cyclo[Lys(COCH2Ph)-Pro]4 (IV) were prepared and the conformational properties and metal ion-binding properties of these cyclic peptides were studied. Metal-ion binding by the side chain polar groups in the cyclic peptides was not observed I-IV formed complexes selectively with Ba2+ ion. III transported Ba2+ and K+ ions efficiently through a liquid membrane, the ability of the owing to ion extraction

IT 82067-64-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and conformation and ion transport properties of)

RN 82067-64-9 HCAPLUS

CN Cyclo(L-α-glutamyl-L-prolyl-L-α-glutamyl-L-prolyl), dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 22

IT 16691-00-2P 82067-55-8P 82067-56-9P 82067-64-9P
82081-23-0P 82213-89-6P 82213-90-9P 82263-43-2P 84739-04-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and conformation and ion transport properties of)

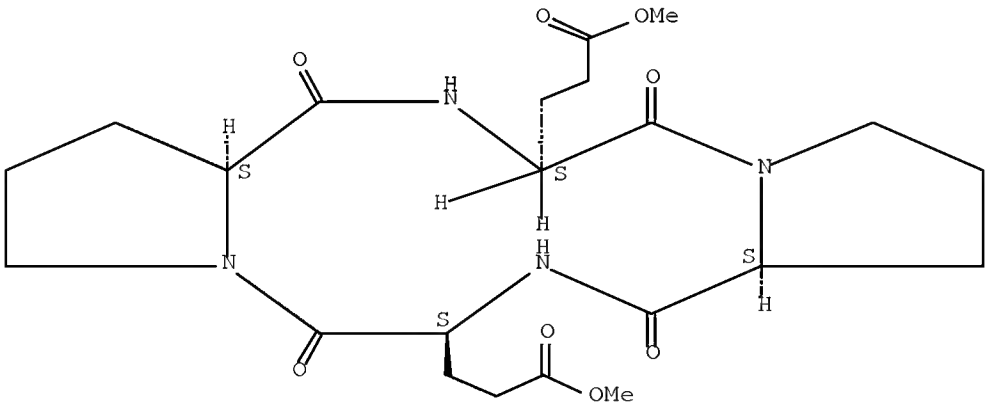
L13 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1982:406765 HCAPLUS Full-text
DOCUMENT NUMBER: 97:6765
ORIGINAL REFERENCE NO.: 97:1311a,1314a
TITLE: Synthesis and interaction with metal ions of cyclic oligopeptides having acidic side chains
AUTHOR(S): Fusaoka, Yoshinari; Kimura, Shunsaku; Imanishi, Yukio
CORPORATE SOURCE: Dep. Polym. Chem., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Peptide Chemistry (1982), Volume Date 1981, 19th, 191-4
CODEN: PECHDP; ISSN: 0388-3698
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclo[Glu(OCH2Ph)-Glu(OMe)] (I), cyclo[Glu-Glu(OMe)] (II), cyclo(Glu-Glu) (III), cyclo[Glu(OMe)-Pro]2 (IV), and cyclo(Glu-Pro)2 (V) were prepared and their solution conformations were determined by CD and 1H and 13C NMR spectroscopy. The ring conformation of the cyclic dipeptides is a flagpole-boat type, whereas the side chains of I and II are folded and those of III are unfolded. In CDCl3 IV has a major C2-sym. conformation with all trans peptide bonds and a minor asym. conformation, whereas V has several different conformations in CDCl3. The interaction of the above cyclic peptides with metals was studied by the above spectroscopy. The side chains of III did not cooperate in binding to Eu3+. IV and V take on asym. conformations without metal ions, whereas the conformations of these peptides converged into C2-sym. conformations upon the addition of an equivalent amount of Ba2+ to a 95 % MeOD solution Consequently, IV and V take a sym. conformation in order to form complexes with metal ions.

IT 82067-64-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and saponification and complexation with metal ions)
RN 82067-64-9 HCAPLUS
CN Cyclo(L-α-glutamyl-L-prolyl-L-α-glutamyl-L-prolyl), dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 22
IT 82067-64-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and saponification and complexation with metal ions)

******* QUERY RESULTS *******
(CLAIM 1)

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=> d his l17

     (FILE 'HCAPLUS' ENTERED AT 15:37:37 ON 04 FEB 2009)
L17          37 S L16 NOT L13


     FILE 'STNGUIDE' ENTERED AT 15:45:53 ON 04 FEB 2009

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L1               STR
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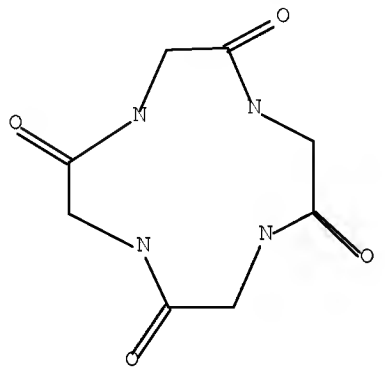
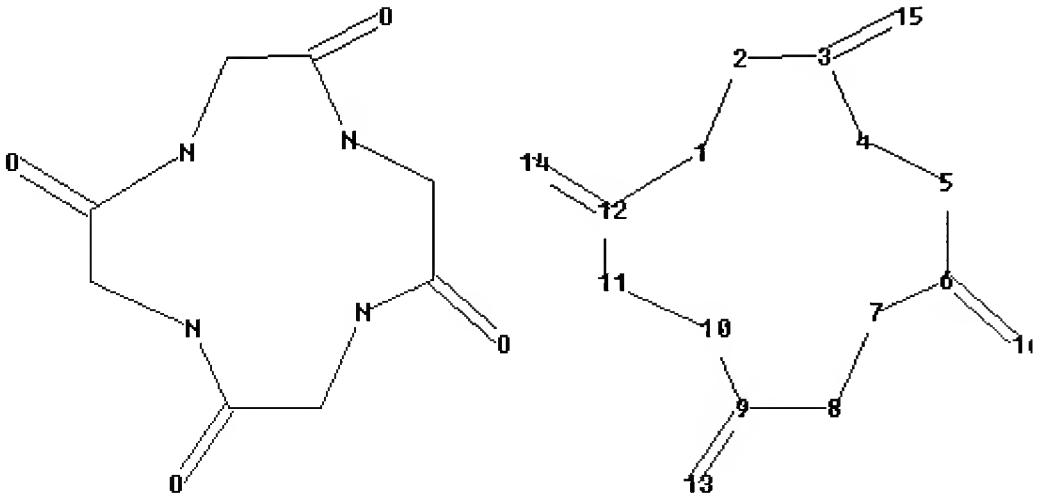


Structure attributes must be viewed using STN Express query preparation:

Uploading L2.str



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chain nodes :
13  14  15  16
ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12
chain bonds :
3-15  6-16  9-13  12-14
ring bonds :
1-2  1-12  2-3  3-4  4-5  5-6  6-7  7-8  8-9  9-10  10-11  11-12
```

exact/norm bonds :
1-2 1-12 2-3 3-4 3-15 4-5 5-6 6-7 6-16 7-8 8-9 9-10 9-13 10-11 11-12
12-14

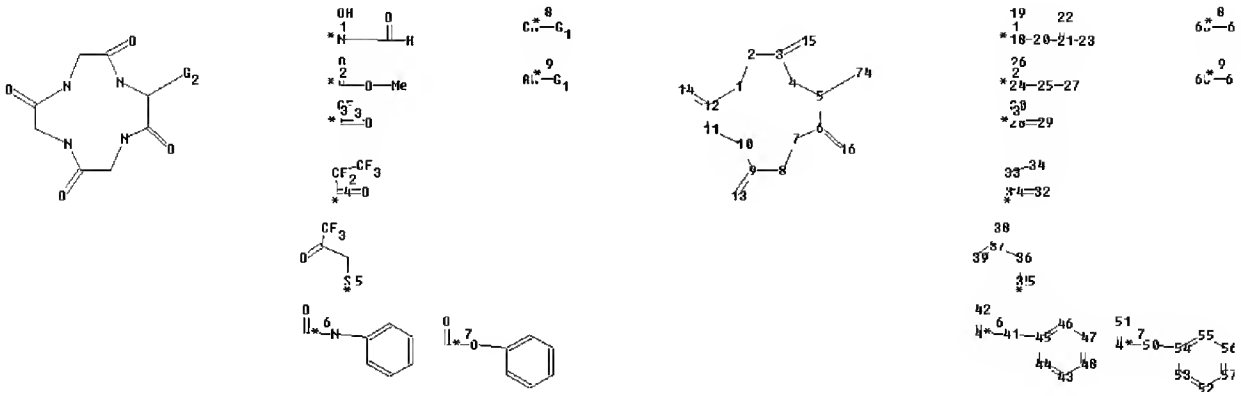
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 16:CLASS

L3 1852 SEA FILE=REGISTRY SSS FUL L1
L4 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation:

Uploading L4.str



chain nodes :
13 14 15 16 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
35 36 37 38 39 40 41 42 49 50 51 66 67 68 69 74
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 43 44 45 46 47 48 52 53 54 55 56
57
chain bonds :
3-15 5-74 6-16 9-13 12-14 18-19 18-20 20-21 21-22 21-23 24-25 24-26 25-
27
28-29 28-30 31-32 31-33 33-34 35-36 36-37 37-38 37-39 40-41 40-42 41-45
49-50 49-51
50-54 66-67 68-69
ring bonds :
1-2 1-12 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 43-44 43-48 44-
45
45-46 46-47 47-48 52-53 52-57 53-54 54-55 55-56 56-57
exact/norm bonds :
1-2 1-12 2-3 3-4 3-15 4-5 5-6 5-74 6-7 6-16 7-8 8-9 9-10 9-13 10-11
11-12 12-14 18-19 18-20 21-22 24-25 24-26 28-29 31-32 35-36 37-39 40-41
40-42 41-45
49-50 49-51 50-54 66-67 68-69
exact bonds :

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20-21  21-23  25-27  28-30  31-33  33-34  36-37  37-38
normalized bonds :
43-44  43-48  44-45  45-46  46-47  47-48  52-53  52-57  53-54  54-55  55-56  56-57

isolated ring systems :
containing 43 : 52 :


G1:[*1],[*2],[*3],[*4],[*5],[*6],[*7]

G2:[*8],[*9]

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:CLASS  14:CLASS  15:CLASS  16:CLASS  18:CLASS  19:CLASS
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74:CLASS

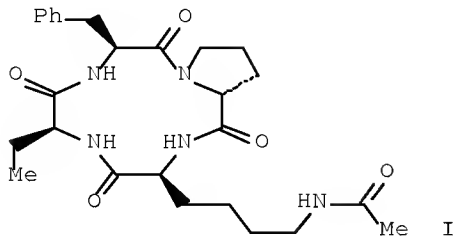



L6           35 SEA FILE=REGISTRY SUB=L3 SSS FUL L4
L7          951 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3
L8           16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6
L9            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  US20070185071/PN
L10       14504 SEA FILE=HCAPLUS ABB=ON  PLU=ON  YOSHIDA M?/AU
L11         618 SEA FILE=HCAPLUS ABB=ON  PLU=ON  NISHINO N?/AU
L12           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L10 OR L11) AND L8) OR (L8
                AND L9)
L13          12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 NOT L12
L14         333 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND 34/SC,SX
L15          45 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 AND HISTONE DEACETYL?
L16          41 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 NOT L12
L17          37 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 NOT L13


=> d l17 1-37 ibib abs fhitstr hitind

L17  ANSWER 1 OF 37  HCAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:462739  HCAPLUS  Full-text
DOCUMENT NUMBER:          149:10273
TITLE:                    Synthesis and biological evaluation of histone
                          deacetylase inhibitors that are based on
                          FR235222: a cyclic tetrapeptide scaffold
AUTHOR(S):                Singh, Erinprit K.; Ravula, Suchitra; Pan, Chung-Mao;
                          Pan, Po-Shen; Vasko, Robert C.; Lapera, Stephanie A.;
                          Weerasinghe, Sujith V. W.; Pflum, Mary Kay H.;
                          McAlpine, Shelli R.
CORPORATE SOURCE:         Department of Chemistry and Biochemistry, San Diego
                          State University, San Diego, CA, 92182, USA
SOURCE:                   Bioorganic & Medicinal Chemistry Letters (2008),
                          18(8), 2549-2554
```

CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 149:10273
GI



I

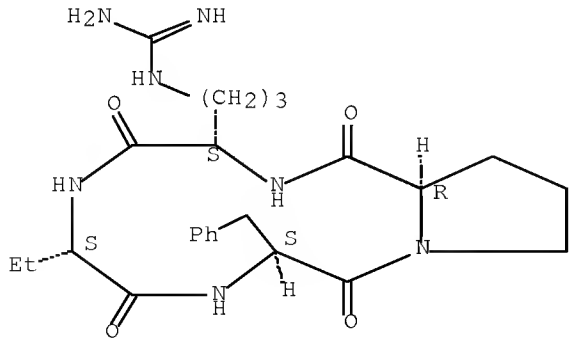
AB The synthesis of six cyclic tetrapeptide as derivs. of FR235222, a recently discovered HDAC inhibitor, is described. These compds. utilized guanidine group as metal coordinators in HDAC inhibitors. In addition, these compds. also showed cytotoxicity, and the most potent compound I was identified. Both inhibition of HDAC inhibitory activity and cytotoxicity against the pancreatic cancer cell line BxPC3 concluded that a guanidine unit can be utilized to inhibit HDAC activity.

IT 1030273-81-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclic tetrapeptides as FR235222 analogs and their histone deacetylase inhibitory and anticancer activity)

RN 1030273-81-4 HCAPLUS

CN Cyclo[(2S)-2-aminobutanoyl-L-phenylalanyl-D-prolyl-L-arginyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

ST cyclic tetrapeptide prepn histone deacetylase inhibitor anticancer

IT Enzyme inhibitors
(histone deacetylase; preparation of cyclic tetrapeptides as FR235222 analogs and their histone deacetylase inhibitory and anticancer activity)
IT Antitumor agents
Macrocyclization
Pancreas, neoplasm
(preparation of cyclic tetrapeptides as FR235222 analogs and their histone deacetylase inhibitory and anticancer activity)
IT Cyclic peptides
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclic tetrapeptides as FR235222 analogs and their histone deacetylase inhibitory and anticancer activity)
IT 1030273-81-4P 1030273-83-6P 1030273-85-8P
1030273-87-0P 1030273-89-2P 1030273-91-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclic tetrapeptides as FR235222 analogs and their histone deacetylase inhibitory and anticancer activity)
IT 2577-90-4 21685-51-8 25528-51-2 27442-39-3 28697-17-8 34306-42-8
37784-17-1 79799-05-6 899442-97-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclic tetrapeptides as FR235222 analogs and their histone deacetylase inhibitory and anticancer activity)
IT 892397-99-8P 1030273-94-9P 1030273-96-1P 1030273-98-3P
1030274-00-0P 1030274-02-2P 1030274-04-4P 1030274-06-6P
1030274-09-9P 1030274-11-3P 1030274-13-5P 1030274-15-7P
1030274-18-0P 1030274-20-4P 1030274-22-6P 1030274-24-8P
1030276-80-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclic tetrapeptides as FR235222 analogs and their histone deacetylase inhibitory and anticancer activity)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:59077 HCAPLUS Full-text
DOCUMENT NUMBER: 148:308613
TITLE: Interaction of aliphatic cap group in inhibition of histone deacetylases by cyclic tetrapeptides
AUTHOR(S): Nishino, Norikazu; Shivashimpi, Gururaj M.; Soni, Preeti B.; Bhuiyan, Mohammed P. I.; Kato, Tamaki; Maeda, Satoko; Nishino, Tomonori G.; Yoshida, Minoru
CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2008), 16(1), 437-445
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

OTHER SOURCE(S): CASREACT 148:308613

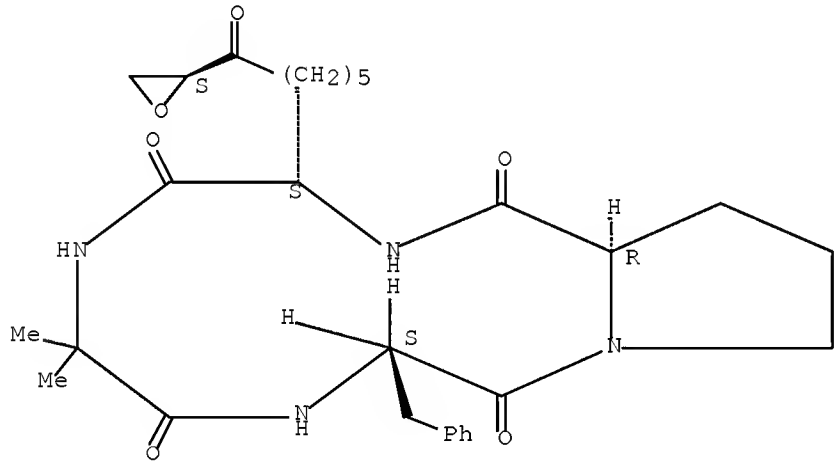
AB Inhibitors of histone deacetylases (HDACs) are a promising class of anticancer agents that effect gene regulation. To know the interaction of aliphatic cap groups with HDACs, cyclic tetrapeptide and bicyclic peptide disulfide hybrids were synthesized without aromatic ring in their macrocyclic framework. Benzene ring of L-Phe in chlamydocin was replaced with several aliphatic amino acids and also a fused bicyclic tetrapeptide was synthesized by ring closing metathesis using Grubb's first generation catalyst. The inhibitory activities of the cyclic peptides against histone deacetylase enzymes were evaluated, which demonstrated most of them are interesting candidates as anticancer agents.

IT 53342-16-8, Chlamydocin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation and biol. activity of structural analogs of chlamydocin as inhibitors of histone deacetylases)

RN 53342-16-8 HCAPLUS

CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7

ST cyclic tetrapeptide prepn histone deacetylase inhibitor structure activity

IT Structure-activity relationship
(enzyme-inhibiting; preparation and structure-activity relationships of cyclic tetrapeptides as inhibitors of histone deacetylases)

IT Antitumor agents
Cyclization
(preparation and structure-activity relationships of cyclic tetrapeptides as inhibitors of histone deacetylases)

IT Cyclic peptides
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and structure-activity relationships of cyclic tetrapeptides as inhibitors of histone deacetylases)

IT Cyclization
Metathesis
(ring-closing metathesis; preparation and structure-activity relationships of cyclic tetrapeptides as inhibitors of histone deacetylases)
IT 53342-16-8, Chlamydocin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation and biol. activity of structural analogs of chlamydocin as inhibitors of histone deacetylases)
IT 300831-21-4P
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and structure-activity relationships of cyclic tetrapeptides as
inhibitors of histone deacetylases)
IT 9076-57-7 952196-95-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation and structure-activity relationships of cyclic tetrapeptides as
inhibitors of histone deacetylases)
IT 960326-28-7P 1009637-36-8P 1009637-37-9P
1009637-38-0P 1009637-47-1P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and structure-activity relationships of cyclic tetrapeptides as
inhibitors of histone deacetylases)
IT 1142-20-7 2127-03-9, 2,2'-Dipyridyldisulfide 4117-09-3 15030-72-5, Cbz-Aib-OH 90071-62-8 102831-44-7 591772-17-7 1009637-57-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and structure-activity relationships of cyclic tetrapeptides as
inhibitors of histone deacetylases)
IT 97372-40-2P 881683-83-6P 881683-84-7P 960326-30-1P 1009637-39-1P
1009637-40-4P 1009637-43-7P 1009637-44-8P
1009637-45-9P 1009637-46-0P 1009637-48-2P
1009637-49-3P 1009637-50-6P 1009637-52-8P 1009637-53-9P
1009637-54-0P 1009637-55-1P 1009637-56-2P 1009637-58-4P
1009637-59-5P 1009637-60-8P 1009637-61-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and structure-activity relationships of cyclic tetrapeptides as
inhibitors of histone deacetylases)
IT 1009637-41-5P 1009637-42-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and structure-activity relationships of cyclic tetrapeptides as
inhibitors of histone deacetylases)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1199737 HCAPLUS Full-text
DOCUMENT NUMBER: 148:79293
TITLE: Design and synthesis of cyclopeptide analogs of the potent histone deacetylase inhibitor FR235222
AUTHOR(S): Gomez-Paloma, Luigi; Bruno, Ines; Cini, Elena;

Khochbin, Saadi; Rodriquez, Manuela; Taddei, Maurizio; Terracciano, Stefania; Sadoul, Karin
CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche, Universita di Salerno, Fisciano, 84084, Italy
SOURCE: ChemMedChem (2007), 2(10), 1511-1519
CODEN: CHEMGX; ISSN: 1860-7179
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English

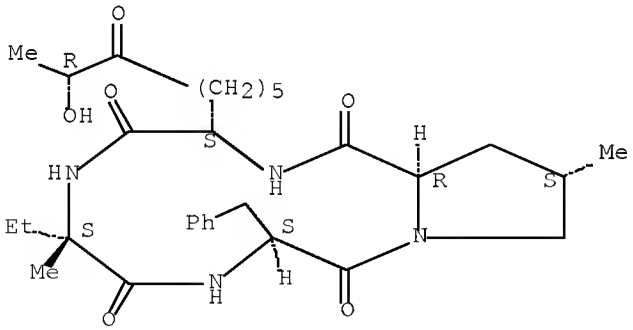
AB Various structurally modified analogs of FR235222, a natural tetrapeptide inhibitor of mammalian histone deacetylases, were prepared in a convergent approach. The design of the compds. was aimed to investigate the effect of structural modifications of the tetrapeptide core involved in enzyme binding in order to overcome some synthetic difficulties connected with the natural product FR235222. The modifications introduced could also help identify key structural features involved in the mechanism of action of these compds. The prepared mols. were subjected to in vitro pharmacol. tests, and their potency was tested on cultured cells. Two of the components of the array were found to be more potent than the parent compound FR235222 and almost as efficient as trichostatin A (TSA). These results demonstrate that it is possible to synthesize highly active cyclic tetrapeptides using com. available amino acids (with the exception of 2-amino-8-oxodecanoic acid, Ahoda). The nature of the residue in the second position of the cyclic peptide and the stereochem. of the Ahoda tail are important for the inhibitory activity of this class of cyclic tetrapeptide analogs.

IT 264259-89-4, FR235222
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

RN 264259-89-4 HCAPLUS

CN Cyclo[(2S,9R)-2-amino-9-hydroxy-8-oxodecanoyl-L-isovalyl-L-phenylalanyl-(4S)-4-methyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7, 9

ST cyclopeptide synthesis histone deacetylase inhibitor FR235222 analog cell proliferation; solid phase peptide synthesis cyclization FR235222 analog; enzyme inhibiting structure activity cyclopeptide; acetylated protein deacetylation histone deacetylase Western blot monoclonal antibody

IT Histones

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H4; solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

IT Structure-activity relationship
(enzyme-inhibiting; solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

IT Solid phase synthesis
(peptide; solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

IT Animal cell line
Cyclization
Deacetylation
Enzyme inhibitors
Natural products
(solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

IT Cyclic peptides
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

IT 9076-57-7, Histone deacetylase 58880-19-6, Trichostatin A 264259-89-4, FR235222 960156-18-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

IT 157618-75-2P 561045-20-3P 960156-08-5P 960156-09-6P 960156-11-0P 960156-13-2P 960156-15-4P 960156-16-5P 960156-17-6P 960287-39-2P 960287-41-6P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

IT 162648-54-6 175453-08-4 857478-30-9 960156-19-8 960156-20-1 960156-21-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(solid phase synthesis and structure-activity relationship of cyclopeptide analogs of potent histone deacetylase inhibitor FR235222)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1195240 HCAPLUS Full-text
DOCUMENT NUMBER: 148:79292
TITLE: Molecular design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework
AUTHOR(S): Shivashimpi, Gururaj M.; Amagai, Satoshi; Kato, Tamaki; Nishino, Norikazu; Maeda, Satoko; Nishino, Tomonori G.; Yoshida, Minoru
CORPORATE SOURCE: Graduate School of Life Science and Systems

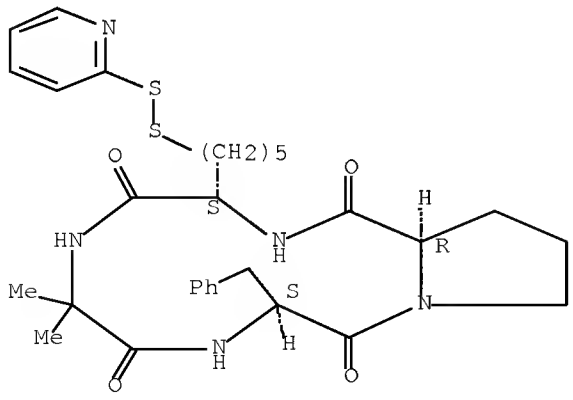
Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(24), 7830-7839
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 148:79292

AB Chlamydocin, a cyclic tetrapeptide containing aminoisobutyric acid (Aib), L-phenylalanine (L-Phe), D-proline (D-Pro), and a unique amino acid L-2-amino-8-oxo-9,10-epoxydecanoic acid, inhibits the histone deacetylases (HDACs), a class of enzymes, which play important roles in regulation of gene expression. Sulfur containing amino acids can also inhibit potently, so zinc ligand, such as sulfhydryl group connected with a linker to the so-called capping group, corresponding to cyclic tetrapeptide framework in case of chlamydocin is supposed to interact with the surface of HDAC mol. Various changes in amino acid residues in chlamydocin may afford specific inhibitors toward HDAC paralogs. To find out specific inhibitors, we focused on benzene ring of L-Phe in chlamydocin framework to shift to various parts of cyclic tetrapeptide. We prepared and introduced several aromatic amino acids into the cyclic tetrapeptides. By evaluating inhibitory activity of these macrocyclic peptides against HDACs, we could find potent inhibitors by shifting the aromatic ring to the Aib site.

IT 952196-95-1P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity relationship)

RN 952196-95-1 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S)-2-amino-7-(2-pyridinyldithio)heptanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 3, 7, 22

ST cyclic tetra peptide synthesis histone deacetylase inhibitor gene expression; histone deacetylase inhibiting structure activity cyclopeptide chlamydocin analog; peptide

coupling cyclization conformation CD

IT Enzyme inhibitors
Sulfhydryl group
(design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity relationship)

IT Cyclic peptides
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity relationship)

IT Pochonia chlamydosporia
(design of histone deacetylase inhibitors, chlamydocin analogs, their synthesis and structure-activity relationship)

IT Animal cell line
Gene expression
Human
(design of regulating gene expression histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis and structure-activity relationship)

IT Promoter (genetic element)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(design of regulating gene expression histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis and structure-activity relationship)

IT Conformation
(effect of aromatic ring shifting on conformational change in prepared histone deacetylase inhibitors studied by CD)

IT Structure-activity relationship
(enzyme-inhibiting; design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity relationship)

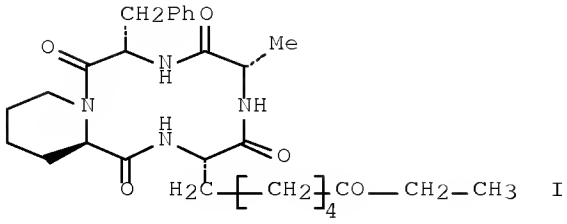
IT 9076-57-7, Histone deacetylase 58880-19-6, Trichostatin A 573719-06-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity relationship)

IT 952196-95-1P 960326-10-7P 960326-11-8P 960326-13-0P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity relationship)

IT 960326-09-4P 960326-14-1P 960326-16-3P 960326-18-5P 960326-20-9P 960326-22-1P 960326-24-3P 960326-26-5P 960326-28-7P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity

relationship)
IT 1142-20-7 1145-80-8 2127-03-9 15030-72-5 20806-43-3 53990-33-3
90071-62-8 91733-75-4 127862-89-9 127862-90-2 154703-82-9
166586-72-7 189094-06-2 591772-17-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity relationship)
IT 97372-40-2P 960326-30-1P 960326-33-4P 960326-36-7P 960326-39-0P
960326-42-5P 960326-44-7P 960326-46-9P 960326-51-6P
960326-53-8P 960326-54-9P 960326-56-1P 960326-58-3P
1009637-53-9P 1020731-17-2P 1020731-51-4P
1020731-86-5P 1020731-95-6P 1020732-23-3P
1020732-50-6P 1020732-61-9P 1020732-62-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design of histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis by peptide coupling, following by cyclization, and structure-activity relationship)
IT 53342-16-8DP, Chlamydocin, analogs
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design of histone deacetylase inhibitors, chlamydocin analogs, their synthesis and structure-activity relationship)
IT 9014-00-0, Luciferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(design of regulating gene expression histone deacetylase inhibitors by aromatic ring shifting in chlamydocin framework, their synthesis and structure-activity relationship)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:602490 HCAPLUS Full-text
DOCUMENT NUMBER: 147:230297
TITLE: Microsporins A and B: new histone deacetylase inhibitors from the marine-derived fungus Microsporum cf. gypseum and the solid-phase synthesis of microsporin A
AUTHOR(S): Gu, Wenxin; Cueto, Mercedes; Jensen, Paul R.; Fenical, William; Silverman, Richard B.
CORPORATE SOURCE: Department of Chemistry, Department of Biochemistry, Molecular Biology, and Cell Biology, Center for Drug Discovery and Chemical Biology, Northwestern University, Evanston, IL, 60208-3113, USA
SOURCE: Tetrahedron (2007), 63(28), 6535-6541
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 147:230297
GI



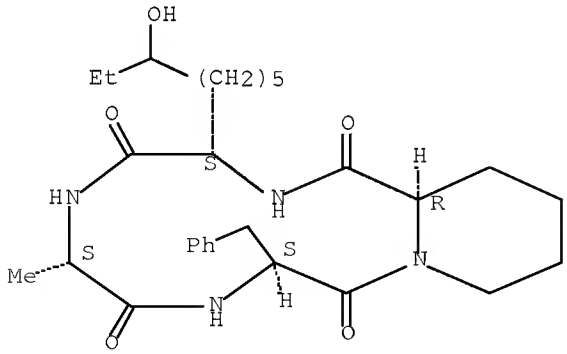
AB Two new cyclic peptides, microsporins A (I) and B, were isolated from culture exts. of the marine-derived fungus Microsporum cf. gypseum obtained from a sample of the bryozoan Bugula sp. collected in the U.S. Virgin Islands. The structures of the new compds. were determined by extensive interpretation of 2D NMR data and by chemical methods. Microsporins A and B are potent inhibitors of histone deacetylase and demonstrate cytotoxic activity against human colon adenocarcinoma (HCT-116), as well as against the National Cancer Institute 60 cancer cell panel. The total synthesis of microsporin A on solid-phase is also reported.

IT 945491-39-4P, Microsporin B
RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

RN 945491-39-4 HCAPLUS

CN Cyclo[L-alanyl-L-phenylalanyl-(2R)-2-piperidinecarbonyl-(2S)-2-amino-8-hydroxydecanoyl] (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Currently available stereo shown.



CC 10-1 (Microbial, Algal, and Fungal Biochemistry)
Section cross-reference(s): 1, 7, 34

ST microsporin natural product Microsporum histone deacetylase inhibitor antitumor; prepn microsporin A Microsporum

IT Human
(cell line; microsporins A and B are new histone

deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT Adenocarcinoma
(colon adenocarcinoma; microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT Intestine, neoplasm
(colon, adenocarcinoma; microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT Antitumor agents
Microsporum gypseum
(microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT Porins
RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(microsporins; microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT Nomenclature
(new natural products; microsporins A and B (cyclic tetrapeptides), new histone deacetylase inhibitors from marine-derived fungus Microsporum cf. gypseum)

IT Molecular structure, natural product
(of microsporins A and B (cyclic tetrapeptides), new histone deacetylase inhibitors from marine-derived fungus Microsporum cf. gypseum)

IT Cyclic peptides
RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(tetrapeptides; microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT 149647-78-9, SAHA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(histone deacetylase inhibition by, comparison with; microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT 945491-39-4P, Microsporin B
RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PAC (Pharmacological activity); PRP (Properties); PUR

(Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT 945491-38-3P, Microsporin A
RL: BSU (Biological study, unclassified); NPO (Natural product occurrence); PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT 35661-39-3 35661-40-6 86069-86-5 635680-16-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

IT 335637-29-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(microsporins A and B are new histone deacetylase inhibitors with cytotoxic activity from marine-derived fungus Microsporum cf. gypseum and solid-phase synthesis of microsporin A)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:162263 HCAPLUS Full-text
DOCUMENT NUMBER: 148:332007
TITLE: Ring-closing metathesis in the synthesis of biologically active peptidomimetics of apicidin A
AUTHOR(S): Deshmukh, Prashant H.; Schulz-Fademrecht, Carsten; Procopiou, Panayiotis A.; Vigushin, David A.; Coombes, R. Charles; Barrett, Anthony G. M.
CORPORATE SOURCE: Department of Chemistry, Imperial College London, London, SW7 2 AY, UK
SOURCE: Advanced Synthesis & Catalysis (2007), 349(1+2), 175-183
CODEN: ASCAF7; ISSN: 1615-4150
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 148:332007

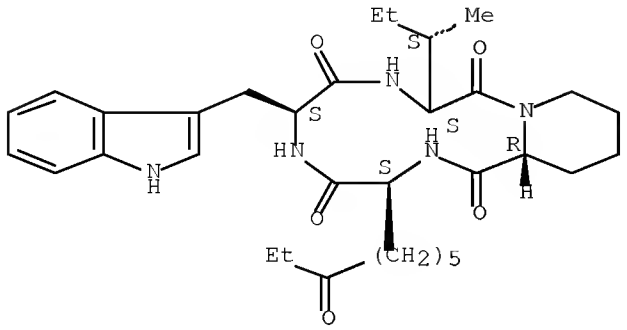
AB The synthesis of novel 16-membered macrocyclic peptidomimetics are reported, which employ iterative peptide coupling followed by high yielding ring-closing metathesis (RCM) as the key cyclization step. The target macrocyclic compds. include compds. containing a (2S)-amino-8-oxodecanoic acid (Aoda) residue as analogs of apicidin A s [i.e., cyclo[(2S)-2-amino-8-oxodecanoyl-L-tryptophyl-L-isoleucyl-(2R)-2- piperidinecarbonyl]] which is a known potent histone deacetylase (HDAC) inhibitor. These showed modest levels of biol. activity as HDAC inhibitors.

IT 183506-67-4DP, Apicidin A, peptidomimetic analogs
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of peptidomimetics of apicidin A and study of their activity as
histone deacetylase inhibitors)

RN 183506-67-4 HCAPLUS
CN Cyclo[(2S)-2-amino-8-oxodecanoyl-L-tryptophyl-L-isoleucyl-(2R)-2-

piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST cyclization macrocyclic compd medicinal chem metathesis peptidomimetic prepn; apicidin peptidomimetic prepn histone deacetylase inhibitor
IT Peptidomimetics
(cyclic; preparation of peptidomimetics of apicidin A and study of their activity as histone deacetylase inhibitors)
IT Cyclic peptides
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(peptidomimetic; preparation of peptidomimetics of apicidin A and study of their activity as histone deacetylase inhibitors)
IT 9076-57-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of peptidomimetics of apicidin A and study of their
activity as histone deacetylase inhibitors)
IT 1011481-89-2P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptidomimetics of apicidin A and study of their activity as
histone deacetylase inhibitors)
IT 183506-67-4DP, Apicidin A, peptidomimetic analogs 1011481-90-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of peptidomimetics of apicidin A and study of their activity as
histone deacetylase inhibitors)
IT 591-80-0, 4-Pentenoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of peptidomimetics of apicidin A and study of their activity as
histone deacetylase inhibitors)
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN

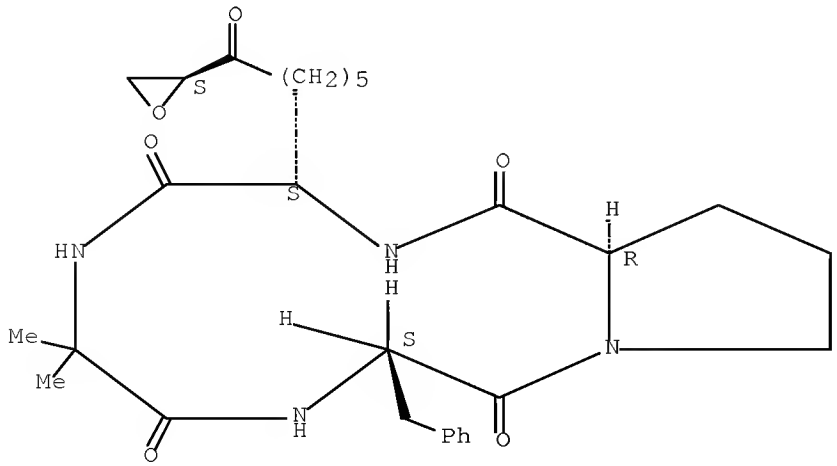
ACCESSION NUMBER: 2007:70089 HCAPLUS Full-text
DOCUMENT NUMBER: 148:403546
TITLE: Aromatic ring shifting in chlamydocin framework for specific inhibition of histone deacetylase paralogs
AUTHOR(S): Shivashimpi, Gururaj M.; Amagai, Satoshi; Kato, Tamaki; Nishino, Norikazu; Nakagawa, Junichi; Maeda, Satoko; Nishino, Tomonori G.; Yoshida, Minoru
CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan
SOURCE: Peptide Science (2006), 43rd, 268-269
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Japanese Peptide Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, amino-2-indane carboxylic acid (A2in), DL-amino-1-indane carboxylic acid (DL-A1in), and DL-2-Me phenylalanine (2MePhe) were prepared and introduced into the cyclic tetrapeptide. When cyclic tetrapeptides were obtained as diastereomeric mixture, they were successfully separated by chromatog. Six cyclic tetrapeptides were designed by introducing various unusual amino acids, where Am7(S2Py) is 2-amino-7-[(2-pyridinyl)dithio]heptanoyl. The thiol function is protected as disulfide hybrid. The synthesized cyclic tetrapeptides were assayed for HDAC inhibitory activity using HDAC1, HDAC2 and HDAC6 prepared from 293T cells. These compds. showed HDAC inhibitory activity in nanomolar scale and one compound containing D-A1in was shown to have very potent activity in vitro and in vivo. Proceedings of the International Conference of 43rd Japanese Peptide Symposium and 4th Peptide Engineering Meeting (43JPS/PEM4), Yokohama, Japan, Nov. 5-8, 2006.

IT 53342-16-8DP, Chlamydocin, analogs
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclo[methylalanyl-L-phenylalanyl-D-prolyl-(amino)[(pyridinyl)dithio]heptanoyl] tetrapeptides (chlamydocin indene and isoquinoline analogs) and study of their activity as inhibitors of histone deacetylase paralogs)

RN 53342-16-8 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST benzene ring shift chlamydocin framework histone deacetylase inhibitor anticancer
IT Cyclic peptides
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cyclotetrapeptides; preparation of cyclo[methylalanyl-L-phenylalanyl-D-prolyl- (amino)[(pyridinyl)dithio]heptanoyl] tetrapeptides (chlamydocin indene and isoquinoline analogs) as inhibitors of histone deacetylase paralogs)
IT Antitumor agents
(preparation of cyclo[methylalanyl-L-phenylalanyl-D-prolyl-(amino)[(pyridinyl)dithio]heptanoyl] tetrapeptides (chlamydocin indene and isoquinoline analogs) and study of their activity as inhibitors of histone deacetylase paralogs)
IT 9076-57-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of cyclo[methylalanyl-L-phenylalanyl-D-prolyl-(amino)[(pyridinyl)dithio]heptanoyl] tetrapeptides (chlamydocin indene and isoquinoline analogs) and study of their activity as inhibitors of histone deacetylase paralogs)
IT 53342-16-8DP, Chlamydocin, analogs 960326-09-4P 960326-10-7P 960326-11-8P 960326-13-0P 960326-14-1P 960326-16-3P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclo[methylalanyl-L-phenylalanyl-D-prolyl-(amino)[(pyridinyl)dithio]heptanoyl] tetrapeptides (chlamydocin indene and isoquinoline analogs) and study of their activity as inhibitors of histone deacetylase paralogs)
IT 2127-03-9 3927-71-7 22888-51-3, 2-Methyl phenylalanine 27473-62-7 591772-17-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclo[methylalanyl-L-phenylalanyl-D-prolyl-(amino)[(pyridinyl)dithio]heptanoyl] tetrapeptides (chlamydocin indene and isoquinoline analogs) and study of their activity as inhibitors of histone deacetylase paralogs)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:70080 HCAPLUS Full-text
DOCUMENT NUMBER: 148:379945
TITLE: Design and synthesis of histone deacetylase inhibitors containing hydroxy-imino-acids as the capping group
AUTHOR(S): Hirashima, Yoshinori; Watanabe, Louis A.; Bhuiyan, Mohammed P. I.; Kato, Tamaki; Nishino, Norikazu; Nakagawa, Junichi; Maeda, Satoko; Nishino, Tomonori G.; Yoshida, Minoru
CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan
SOURCE: Peptide Science (2006), 43rd, 255-256
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Japanese Peptide Society

DOCUMENT TYPE: Journal
LANGUAGE: English

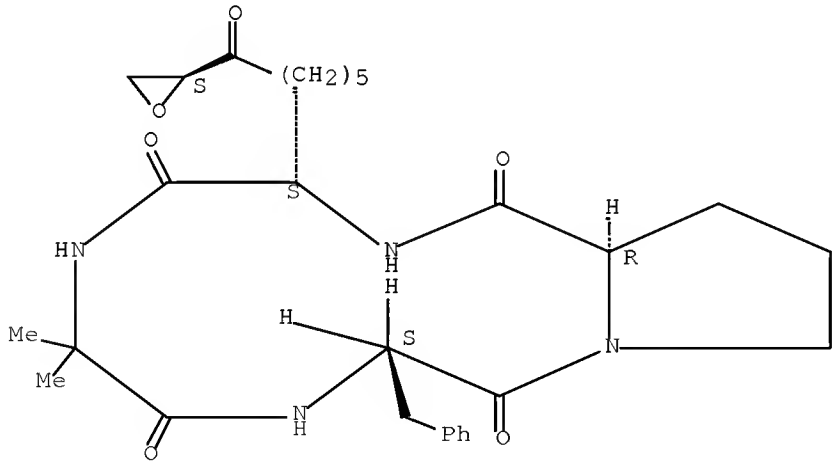
AB Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription. Chlamydocin was originally isolated from the fungus Diheterospora chlamydospora and has been shown to exhibit potent anticancer activity in vitro. In the present study, a chlamydocin analog, sulfur-containing cyclic peptide (SCOP), was modified by introducing various hydroxy-imino-acids as the capping groups. D-cis- and trans-hydroxyproline (Hypro) and D-cis- and trans-hydroxypipecolic acid (Hypip) derivs. were prepared and incorporated into cyclic tetrapeptides. The chlamydocin analogs having disulfide group with four different hydroxy-imino-acids may be useful in distinguishing the surface of HDAC paralogs and may perform specific inhibition. Chlamydocin derivs. thus prepared included cyclo[2-methylalanyl-L-phenylalanyl-D-4-(hydroxy)prolyl-2-amino-7-[(2- pyridinyl)dithio]heptanoyl] isomers and Cyclo[2-methylalanyl-L-phenylalanyl-(2R)-5-hydroxy-2-piperidinecarbonyl-2- amino-7-[(2-pyridinyl)dithio]heptanoyl] isomers. Proceedings of the International Conference of 43rd Japanese Peptide Symposium and 4th Peptide Engineering Meeting (43JPS/PEM4), Yokohama, Japan, Nov. 5-8, 2006.

IT 53342-16-8DP, Chlamydocin, analogs and derivs.
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs (chlamydocin analogs) capable of distinguishing between histone deacetylase paralogs)

RN 53342-16-8 HCAPLUS

CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)

ST histone deacetylase inhibitor hydroxy imino acid capping Diheterospora

IT Peptides, preparation
RL: SPN (Synthetic preparation); PREP (Preparation)
(analogs, cyclotetrapeptides; preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs (chlamydocin analogs) capable of distinguishing between histone

deacetylase paralogs)
IT Post-transcriptional processing
(capping; preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-
amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs
(chlamydocin analogs) capable of distinguishing between histone deacetylase paralogs)
IT Cyclic peptides
RL: SPN (Synthetic preparation); PREP (Preparation)
(cyclotetrapeptides, analogs; preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs (chlamydocin analogs) capable of distinguishing between histone deacetylase paralogs)
IT Antitumor agents
Asymmetric synthesis and induction
Pochonia chlamydosporia
(preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs (chlamydocin analogs) capable of distinguishing between histone deacetylase paralogs)
IT 9076-57-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs (chlamydocin analogs) capable of distinguishing between histone deacetylase paralogs)
IT 2127-03-9, 2,2'-Dithiobis(pyridine) 10387-40-3, Potassium thioacetate
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs (chlamydocin analogs) capable of distinguishing between histone deacetylase paralogs)
IT 1013400-21-9P 1013400-23-1P 1013400-25-3P 1013400-27-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs (chlamydocin analogs) capable of distinguishing between histone deacetylase paralogs)
IT 53342-16-8DP, Chlamydocin, analogs and derivs.
1013400-29-7P 1013400-31-1P 1013400-33-3P
1013400-36-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of cyclo[methylalanyl-L-phenylalanyl(hydroxy)-D-prolyl-amino[(pyridinyl)dithio]heptanoyl] stereoisomers and homologs (chlamydocin analogs) capable of distinguishing between histone deacetylase paralogs)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:711073 HCAPLUS Full-text
DOCUMENT NUMBER: 145:336290
TITLE: Synthesis of L-2-amino-8-oxodecanoic acid: an amino acid component of apicidins
AUTHOR(S): Linares, M. Lourdes; Agejas, F. Javier; Alajarin, Ramon; Vaquero, J. Jose; Alvarez-Builla, Julio
CORPORATE SOURCE: Departamento de Quimica Organica, Universidad de Alcala, Madrid, 28871, Spain

SOURCE: Synthesis (2006), (12), 2069-2073
CODEN: SYNTBF; ISSN: 0039-7881
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:336290

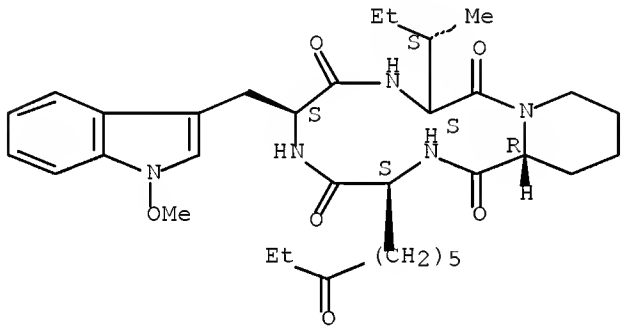
AB The synthesis of L-2-amino-8-oxodecanoic acid (Aoda) is described. This is a rare amino acid component of apicidins, a family of new cyclic tetrapeptides, inhibitors of histone deacetylase. Aoda was synthesized in seven steps from L-glutamic acid, via Wittig reaction and basic hydrolysis, along with some derivs.

IT 183506-66-3
RL: BSU (Biological study, unclassified); PNU (Preparation, unclassified); BIOL (Biological study)
(synthesis of amino acid component of apicidins isolated from Fusarium pallidoroseum)

RN 183506-66-3 HCAPLUS

CN Cyclo[(2S)-2-amino-8-oxodecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7, 10

ST aminooxodecanoic acid synthesis apicidin fragment Fusarium pallidoroseum; apicidin histone deacetylase inhibitor; glutamic acid Wittig reaction hydrolysis

IT Enzyme inhibitors
(synthesis of aminooxodecanoic acid as amino acid component of apicidins, inhibitors of histone deacetylase)

IT 28920-43-6, Fmoccl 183506-66-3 183506-67-4, Apicidin A 189337-29-9, Apicidin B 366448-28-4, Apicidin C
RL: BSU (Biological study, unclassified); PNU (Preparation, unclassified); BIOL (Biological study)
(synthesis of amino acid component of apicidins isolated from Fusarium pallidoroseum)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis of aminooxodecanoic acid as amino acid component of apicidins, inhibitors of histone deacetylase)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN

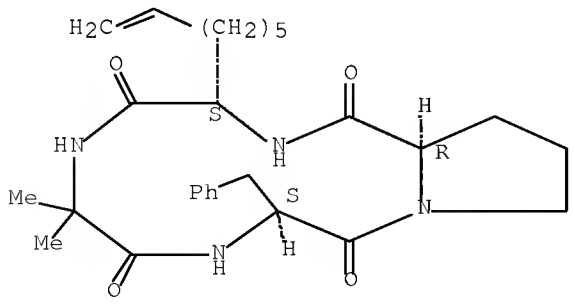
ACCESSION NUMBER: 2006:315083 HCAPLUS Full-text
DOCUMENT NUMBER: 144:483405
TITLE: Chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylases
AUTHOR(S): Bhuiyan, Mohammed P. I.; Kato, Tamaki; Okauchi, Tatsuo; Nishino, Norikazu; Maeda, Satoko; Nishino, Tomonori G.; Yoshida, Minoru
CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2006), 14(10), 3438-3446
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:483405

AB A series of chlamydocin analogs with various carbonyl functionalities were designed and synthesized as histone deacetylase (HDAC) inhibitors. Chlamydocin is a cyclic tetrapeptide containing an epoxyketone surrogate in the side chain which makes it irreversible inhibitor of HDACs, whereas apicidins are a class of cyclic tetrapeptides that contain an ethylketone moiety as zinc ligand. We replaced the epoxyketone moiety of chlamydocin with several ketones and aldehyde to synthesize potent reversible and selective HDAC inhibitors. The inhibitory activity of the cyclic tetrapeptides against histone deacetylase enzymes were evaluated and the result showed most of them are potent inhibitors. Some of them have remarkable selectivity among the HDACs.

IT 887277-64-7P
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylases)

RN 887277-64-7 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S)-2-amino-8-nonenoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 7-3 (Enzymes)
Section cross-reference(s): 6, 34
ST histone deacetylase zinc chlamydocin ligand
IT Structure-activity relationship

(enzyme-inhibiting, histone deacetylase;
chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylases)

IT 7440-66-6, Zinc, biological studies 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylases)

IT 887277-64-7P 887277-65-8P 887277-67-0P 887277-69-2P
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylases)

IT 53342-16-8DP, Chlamydocin, analogs 536753-42-1P 887277-68-1P 887277-72-7P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylases)

IT 1161-13-3 15030-72-5 18162-48-6, TBDMS chloride 184719-80-0 300831-21-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylases)

IT 162757-06-4P 221186-79-4P 221186-91-0P 291312-77-1P 887277-60-3P 887277-61-4P 887277-63-6P 887277-66-9P 887277-70-5P 887277-71-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(chlamydocin analogs bearing carbonyl group as possible ligand toward zinc atom in histone deacetylases)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:85544 HCAPLUS Full-text
DOCUMENT NUMBER: 144:312319
TITLE: Total synthesis, NMR solution structure, and binding model of the potent histone deacetylase inhibitor FR235222
AUTHOR(S): Rodriquez, Manuela; Terracciano, Stefania; Cini, Elena; Settembrini, Giulia; Bruno, Ines; Bifulco, Giuseppe; Taddei, Maurizio; Gomez-Paloma, Luigi
CORPORATE SOURCE: Dipartimento Farmaco Chimico Tecnologico Universita di Siena, Siena, 53100, Italy
SOURCE: Angewandte Chemie, International Edition (2006), 45(3), 423-427
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:312319

AB Cyclopeptide FR235222 isolated from the fermentation broth of Acremonium sp. exhibited a potent inhibition of HDAC (mammalian histone deacetylase), has been synthesized. The first key intermediate for the synthesis of of cyclopeptide, (2S,9R)-2-amino-9-hydroxy-8-oxodecanoic acid (Ahoda), was prepared from L-Glu via Wittig-Horner-Emmons reaction, and the second key intermediate, trans-4-methyl-D-proline (4-MePro), was prepared via

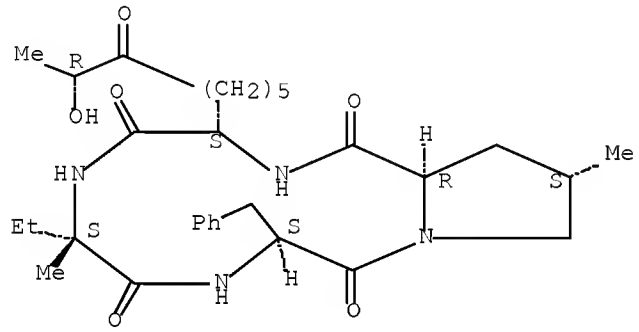
stereoselective methylation and lactamization. A 3D model for cyclopeptide inhibitor interaction with the HDAC active site highlights the differences between the binding mode of small-mol. and cyclopeptide inhibitors.

IT 264259-89-4P, FR235222
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mol. structure of; total synthesis of cyclopeptide FR235222 by solid phase peptide synthesis and macrolactamization, its NMR solution structure and binding to HDAC active site)

RN 264259-89-4 HCAPLUS

CN Cyclo[(2S,9R)-2-amino-9-hydroxy-8-oxodecanoyl-L-isovalyl-L-phenylalanyl-(4S)-4-methyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7, 10, 22

ST cyclopeptide FR235222 total synthesis histone deacetylase inhibitor; solid phase peptide synthesis macrolactamization; aminohydroxy oxodecanoic acid methyl proline asym synthesis; glutamic acid Wittig Horner Emmons reaction stereoselective methylation lactamization; conformation NMR active site HDAC mol structure MD simulation

IT Simulation and Modeling
(mol. dynamics; NMR solution conformation and binding model by MD simulation of potent histone deacetylase inhibitor cyclopeptide FR235222)

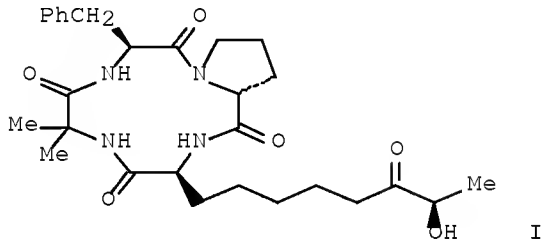
IT Conformation
Enzyme inhibitors
(total synthesis, NMR solution conformation and binding model of potent histone deacetylase inhibitor cyclopeptide FR235222)

IT 264259-89-4P, FR235222
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mol. structure of; total synthesis of cyclopeptide FR235222 by solid phase peptide synthesis and macrolactamization, its NMR solution structure and binding to HDAC active site)

IT 9076-57-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(total synthesis, NMR solution structure and binding model of potent histone deacetylase inhibitor cyclopeptide FR235222)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1260419 HCAPLUS Full-text
DOCUMENT NUMBER: 144:171232
TITLE: Synthesis of 2-Amino-8-oxodecanoic Acids (Aodas) Present in Natural Histone Deacetylase Inhibitors
AUTHOR(S): Rodriquez, Manuela; Bruno, Ines; Cini, Elena; Marchetti, Mauro; Taddei, Maurizio; Gomez-Paloma, Luigi
CORPORATE SOURCE: Istituto di Chimica Biomolecolare, CNR, Sassari, 07040, Italy
SOURCE: Journal of Organic Chemistry (2006), 71(1), 103-107
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:171232
GI



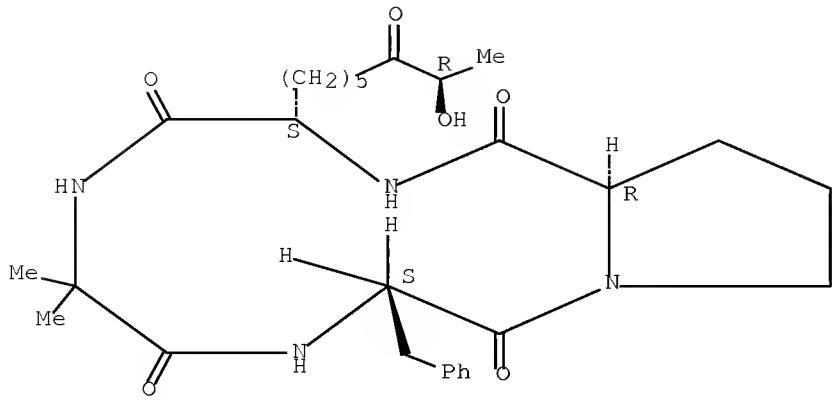
I

AB Differently substituted 2-amino-8-oxodecanoic acids (Aodas), present in naturally occurring inhibitors of histone deacetylase (HDAC), have been prepared using a convergent approach. The configuration in locant 2 of Aodas was derived from enantiomerically pure allylglycine or glutamic acid, whereas the stereochem. of the substituent in locant 9 was derived from either (R)- or (S)-lactic acid or its glyceraldehyde derivative Starting from allylglycine, (2S,9S)- and (2S,9R)-Aodas, protected at the nitrogen as Boc or Fmoc, were obtained in four steps in about 30% overall yield. (2S,9R)-Aoda was used to prepare a cyclic peptide I, a simplified analog of a natural cyclic tetrapeptide inhibitor of histone deacetylase, by solid-phase peptide synthesis. I showed an IC50 = 10 mM when tested against class III HDACs.

IT 157618-75-2P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and biol. activity of an (amino)oxodecanoic acid-containing cyclic peptide as an inhibitor of histone deacetylase)

RN 157618-75-2 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S,9R)-2-amino-9-hydroxy-8-oxodecanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7
ST aminooxodecanoic acid prepn cyclic peptide inhibitor histone deacetylase
IT Peptides, preparation
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cyclic; preparation and biol. activity of an (amino)oxodecanoic acid-containing
cyclic peptide as an inhibitor of histone deacetylase
)
IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation and biol. activity of an (amino)oxodecanoic acid-containing cyclic
peptide as an inhibitor of histone deacetylase)
IT 157618-75-2P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and biol. activity of an (amino)oxodecanoic acid-containing cyclic
peptide as an inhibitor of histone deacetylase)
IT 35661-40-6 94744-50-0 101555-62-8 101555-62-8D, resin-bound
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and biol. activity of an (amino)oxodecanoic acid-containing cyclic
peptide as an inhibitor of histone deacetylase)
IT 874384-21-1DP, resin-bound 874384-22-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and biol. activity of an (amino)oxodecanoic acid-containing cyclic
peptide as an inhibitor of histone deacetylase)
IT 56-86-0, L-Glutamic acid, reactions 105-37-3 4009-98-7 16338-48-0
52373-72-5 82911-69-1 87681-24-1 845641-41-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of (amino)oxodecanoic acids that are present in naturally-occurring inhibitors of histone deacetylase
)
IT 41162-15-6P 121998-80-9P 131569-94-3P 167905-35-3P 335637-29-1P
375858-14-3P 850209-98-2P 850209-99-3P 874384-01-7P 874384-02-8P
874384-03-9P 874384-04-0P 874384-05-1P 874384-06-2P 874384-07-3P

874384-08-4P 874384-09-5P 874384-10-8P 874384-11-9P 874384-12-0P
874384-13-1P 874384-15-3P 874384-17-5P 874384-19-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (amino)oxodecanoic acids that are present in naturally-occurring inhibitors of histone deacetylase)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:441921 HCAPLUS Full-text
DOCUMENT NUMBER: 143:115786
TITLE: Total Synthesis of Cyclic Tetrapeptide FR235222, a Potent Immunosuppressant that Inhibits Mammalian Histone Deacetylases
AUTHOR(S): Xie, Weiqing; Zou, Bin; Pei, Duanqing; Ma, Dawei
CORPORATE SOURCE: State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, Peop. Rep. China
SOURCE: Organic Letters (2005), 7(13), 2775-2777
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:115786
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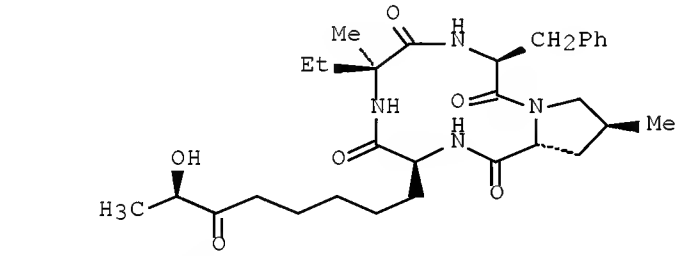
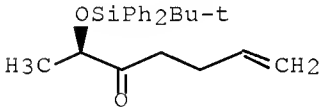
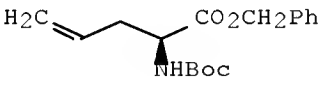


I



II

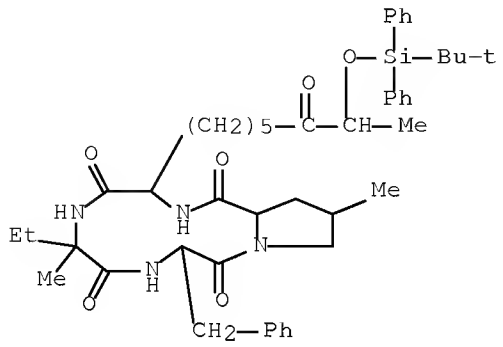


III

AB The total synthesis of FR235222 (I), a potent immunosuppressant with in vivo activities, has been achieved. The key steps include assembling its (2S,9R)-2-amino-9-hydroxy-8-oxodecanoic acid residue via an olefin cross-metathesis of (R)-lactate-derived homoallyl ketone II with protected allyl amino acid III, and constructing the trans-(2R,4S)-4-methylproline unit from protected (R)-pyroglutamic acid in seven steps.

IT 857478-39-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of cyclic tetrapeptide FR235222 using olefin

cross-metathesis reaction as a key step)
RN 857478-39-8 HCAPLUS
CN Cyclo[(2S,9R)-2-amino-9-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-8-oxodecanoyl-L-isovalyl-L-phenylalanyl-(4S)-4-methyl-D-prolyl] (9CI) (CA INDEX NAME)



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
IT 561038-05-9P 857478-12-7P 857478-14-9P 857478-17-2P 857478-19-4P
857478-22-9P 857478-26-3P 857478-28-5P 857478-33-2P 857478-35-4P
857478-37-6P 857478-39-8P 857478-45-6P 857478-47-8P
857478-50-3P 857478-53-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of cyclic tetrapeptide FR235222 using olefin cross-metathesis reaction as a key step)
IT 264259-89-4P 857478-24-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(total synthesis of cyclic tetrapeptide FR235222 using olefin cross-metathesis reaction as a key step)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 14 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:923986 HCAPLUS Full-text
DOCUMENT NUMBER: 142:114462
TITLE: Preparation of apicidin derivatives with inhibiting histone deacetylase activity and cancer metastasis, pharmaceutical compositions
INVENTOR(S): Moon, Aree
PATENT ASSIGNEE(S): S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, No pp. given
CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2002045821	A	20020620	KR 2000-75223	20001211
PRIORITY APPLN. INFO.:			KR 2000-75223	20001211

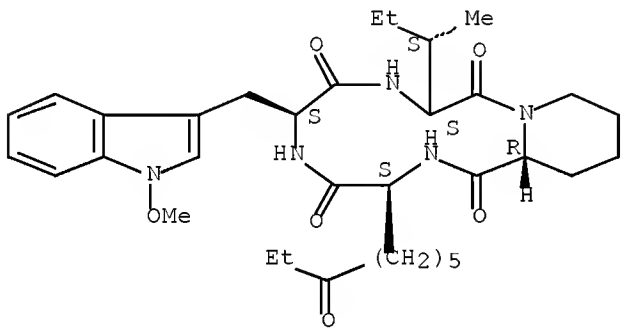
AB Provided are Apicidin derivs. which inhibit cell growth selectively, histone deacetylase(HDAC) activity concentration dependently and MMP-2 activity effectively. And, provided are pharmaceutical compns. containing them and their use for the inhibition of HDAC and cancer metastasis. Apicidin derivative is represented by the formula(1), wherein R is methoxy group; hydroxy group; C2-C6 dialkylamino group; C2-C6 linear or branched hydroxyalkyl; C3-C6 linear or branched dihydroxyalkyl group; C3-C6 alkoxyalkyl group; and substituted or unsubstituted 5 or 6 membered hetero cyclic compound including 1-3 of hetero atoms selected among unsubstituted or C1-C3 alkyl group substituted N, O, and S.

IT 183506-66-3DP, of apicidin derivative
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of apicidin derivs.)

RN 183506-66-3 HCAPLUS

CN Cyclo[(2S)-2-amino-8-oxodecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IC ICM C07D419-14

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 63

ST apicidin deriv prepn histone deacetylase inhibitor anticancer agent

IT 183506-66-3DP, of apicidin derivative
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of apicidin derivs.)

L17 ANSWER 15 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:891777 HCAPLUS Full-text

DOCUMENT NUMBER: 142:74817

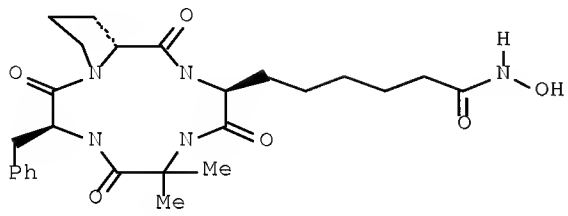
TITLE: Chlamydocin-hydroxamic acid analogues as histone deacetylase inhibitors

AUTHOR(S): Nishino, Norikazu; Jose, Binoy; Shinta, Ryuzo; Kato, Tamaki; Komatsu, Yasuhiko; Yoshida, Minoru

CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan

SOURCE: Bioorganic & Medicinal Chemistry (2004), 12(22), 5777-5784

CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:74817
GI



I

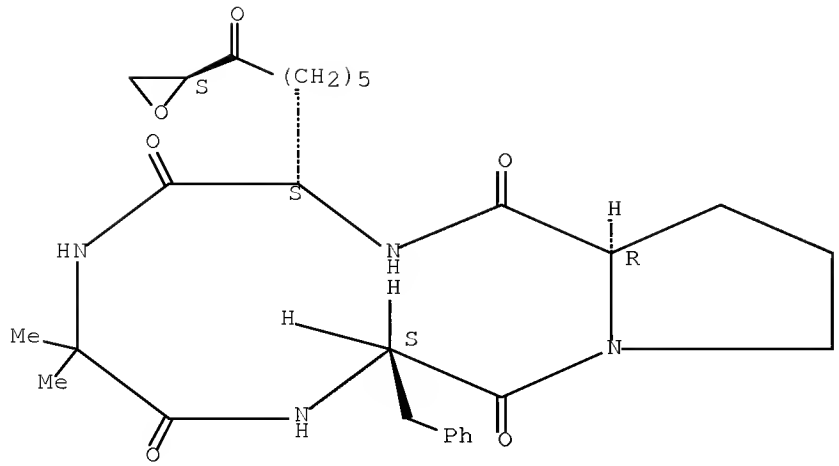
AB Chlamydocin-hydroxamic acid analogs, e.g. I, were designed and synthesized as histone deacetylase (HDAC) inhibitors based on the structure and HDAC inhibitory activity of chlamydocin and trichostatin A. Chlamydocin is a cyclic tetrapeptide containing an epoxyketone moiety in the side chain that makes it an irreversible inhibitor of HDAC. We replaced the epoxyketone moiety of chlamydocin with hydroxamic acid to design potent and reversible inhibitors of HDAC. In addition, a number of amino-cycloalkanecarboxylic acids (Acc) are introduced instead of the simple amino-isobutyric acid (Aib) for a variety of the series of chlamydocin analogs. For example, reacting Z-L-Phe-OH was coupled with H-D-Pro-O-t-Bu to give Z-L-Phe-D-Pro-O-t-Bu which was hydrogenated to remove the Z group, coupled with Z-Aib-OH, and hydrogenated again to give H-Aib-L-PheD-Pro-O-t-Bu. The latter compound was coupled with BocL-Asu(OBzl)-OH and converted to the TFA salt which was cyclized, deprotected and condensed with hydroxylamine hydrochloride to give I in 74% yield. The compds. synthesized were tested for HDAC inhibitory activity and the results showed that many of them are potent inhibitors of HDAC. The replacement of Aib residue of chlamydocin with an aromatic amino acid enhances the in vivo and in vitro inhibitory activity. We have carried out CD and mol. modeling studies on chlamydocin-hydroxamic acid analog and compared it with the solution structure of chlamydocin.

IT 53342-16-8, Chlamydocin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis of chlamydocin-hydroxamic acid analogs, their histone deacetylase inhibitory activity, structure-activity relationship, CD spectra and mol. modeling studies)

RN 53342-16-8 HCAPLUS

CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7, 22

ST chlamydocin hydroxamic acid analog prepn histone deacetylase inhibitor; structure activity chlamydocin hydroxamic acid analog histone deacetylase inhibitor; CD chlamydocin hydroxamic acid analog; mol modeling chlamydocin hydroxamic acid analog

IT Structure-activity relationship
(histone deacetylase-inhibiting; synthesis of chlamydocin-hydroxamic acid analogs, their histone deacetylase inhibitory activity, structure-activity relationship, CD spectra and mol. modeling studies)

IT Circular dichroism
Molecular modeling
(synthesis of chlamydocin-hydroxamic acid analogs, their histone deacetylase inhibitory activity, structure-activity relationship, CD spectra and mol. modeling studies)

IT 9076-57-7 53342-16-8, Chlamydocin 58880-19-6, Trichostatin A
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis of chlamydocin-hydroxamic acid analogs, their histone deacetylase inhibitory activity, structure-activity relationship, CD spectra and mol. modeling studies)

IT 221186-45-4P 291312-80-6P 812667-29-1P
812667-33-7P 812667-35-9P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of chlamydocin-hydroxamic acid analogs, their histone deacetylase inhibitory activity, structure-activity relationship, CD spectra and mol. modeling studies)

IT 291312-79-3P 291312-81-7P 291312-82-8P
291312-83-9P 291312-84-0P 291312-85-1P
291312-86-2P 291312-88-4P 362055-30-9P
362055-31-0P 812667-30-4P 812667-31-5P
812667-32-6P 812667-34-8P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of chlamydocin-hydroxamic acid analogs, their histone deacetylase inhibitory activity, structure-activity relationship, CD spectra and mol. modeling studies)

IT 52-52-8 56-41-7, L-Alanine, reactions 147-85-3, L-Proline, reactions 338-69-2, D-Alanine 535-75-1, 2-Piperidinecarboxylic acid 1161-13-3 2756-85-6 2812-46-6 3160-59-6 3927-71-7 6949-77-5 15030-72-5 27473-62-7 28248-38-6 90071-62-8 174784-95-3 853644-59-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of chlamydocin-hydroxamic acid analogs, their histone deacetylase inhibitory activity, structure-activity relationship, CD spectra and mol. modeling studies)

IT 104849-05-0P 162757-06-4P 221186-79-4P 221186-91-0P 221186-92-1P 286436-68-8P 291312-77-1P 291312-78-2P 812667-36-0P 812667-38-2P 812667-39-3P 812667-40-6P 812667-41-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of chlamydocin-hydroxamic acid analogs, their histone deacetylase inhibitory activity, structure-activity relationship, CD spectra and mol. modeling studies)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

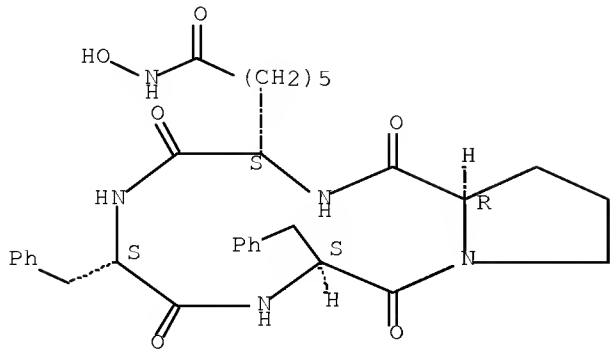
L17 ANSWER 16 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:729351 HCAPLUS Full-text
DOCUMENT NUMBER: 141:390896
TITLE: Subtype Selective Substrates for Histone Deacetylases
AUTHOR(S): Heltweg, Birgit; Dequiedt, Franck; Marshall, Brett L.; Brauch, Carsten; Yoshida, Minoru; Nishino, Norikazu; Verdin, Eric; Jung, Manfred
CORPORATE SOURCE: Department of Pharmaceutical and Medicinal Chemistry, Westfaelische Wilhelms-Universitaet Muenster, Muenster, 48149, Germany
SOURCE: Journal of Medicinal Chemistry (2004), 47(21), 5235-5243
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:390896

AB To probe the steric requirements for deacylation, we synthesized lysine-derived small mol. substrates and examined structure-reactivity relationships with various histone deacetylases. Rat liver, human HeLa, and human recombinant class I and II histone deacetylases (HDACs) as well as human recombinant NAD+-dependent SIRT1 (class III enzyme) were used in these studies. A benzyloxycarbonyl substituent on the α-amino group yielded the highest conversion rates. Replacing the ε-acetyl group with larger lipophilic acyl substituents led to a pronounced decrease in conversion by class I and II enzymes; the class III enzyme displayed a greater tolerance. Incubations with recombinant FLAG-tagged human HDACs 1, 3, and 6 showed a distinct subtype selectivity among small mol. substrates. The subtype selectivity of HDAC inhibitors could be predicted with these substrates and an easily obtainable mixture of HDAC subtypes.

IT 221186-39-6, CHAP 1
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(inhibitor; preparation of subtype selective substrates for histone deacetylases)

RN 221186-39-6 HCAPLUS
CN Cyclo[(2S)-2-amino-8-(hydroxyamino)-8-oxooctanoyl-L-phenylalanyl-L-phenylalanyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry.



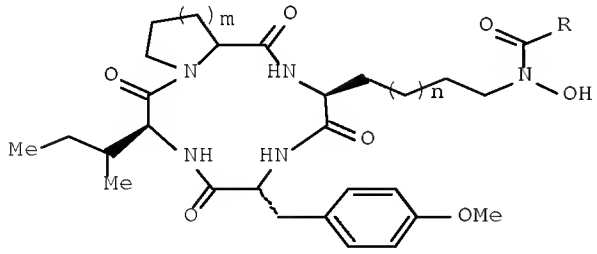
CC 7-3 (Enzymes)
Section cross-reference(s): 26, 34
ST histone deacetylase subtype selective substrate prepn inhibitor
IT Structure-activity relationship
(enzyme substrate, histone deacetylase substrate; preparation of subtype selective substrates for histone deacetylases)
IT Structure-activity relationship
(enzyme-inhibiting, histone deacetylase-inhibiting; preparation of subtype selective substrates for histone deacetylases)
IT Human
Stereochemistry
(preparation of subtype selective substrates for histone deacetylases)
IT 69700-07-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(formation; preparation of subtype selective substrates for histone deacetylases)
IT 438496-81-2, Sirtuin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hSIRT1; preparation of subtype selective substrates for histone deacetylases)
IT 58880-19-6 193551-00-7 209783-80-2, MS-275 221186-39-6, CHAP 1 221186-45-4, CHAP 15 221186-64-7, CHAP 31 251456-60-7 251456-63-0 537049-41-5, Histacin
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(inhibitor; preparation of subtype selective substrates for histone deacetylases)
IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of subtype selective substrates for histone deacetylases)
IT 233691-67-3P 263368-34-9P 642463-22-7P 787549-18-2P 787549-19-3P 787549-20-6P 787549-21-7P 787549-22-8P 787549-23-9P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of subtype selective substrates for histone deacetylases)

IT 79-03-8, Propionyl chloride 103-80-0, Phenacetyl chloride 109-02-4, N-Methyl-morpholine 141-75-3, Butyryl chloride 407-25-0, Trifluoroacetic anhydride 2212-75-1, N-α-Benzyloxycarbonyl-L-lysine 6404-26-8 26093-31-2 53518-15-3 70671-54-4 71989-26-9 159766-56-0 259195-58-9 313052-02-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of subtype selective substrates for histone deacetylases)

IT 14905-30-7P 68223-08-5P 80442-87-1P 787549-17-1P 787549-24-0P 787549-25-1P 787549-26-2P 787549-27-3P 787549-28-4P 787549-29-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of subtype selective substrates for histone deacetylases)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 17 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:346236 HCAPLUS Full-text
DOCUMENT NUMBER: 141:140744
TITLE: Synthesis and histone deacetylase inhibitory activity of cyclic tetrapeptides containing a retrohydroxamate as zinc ligand
AUTHOR(S): Nishino, Norikazu; Yoshikawa, Daisuke; Watanabe, Louis A.; Kato, Tamaki; Jose, Binoy; Komatsu, Yasuhiko; Sumida, Yuko; Yoshida, Minoru
CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(10), 2427-2431
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:140744
GI



I

AB Cyclic tetrapeptide retrohydroxamic acids I (m = 1, 2; n = 1, 2, 3; R = H, Me) were prepared as histone deacetylase (HDAC) inhibitors. The results show that they have potential as anticancer drugs.

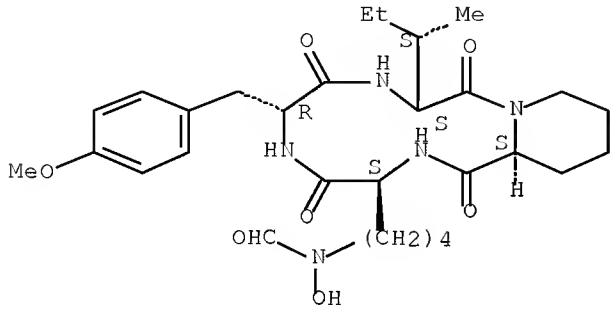
IT 727425-92-5P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and histone deacetylase inhibitory activity of potential antitumor cyclic tetrapeptides containing retrohydroxamate as zinc ligand)

RN 727425-92-5 HCAPLUS

CN Cyclo[L-isoleucyl-(2S)-2-piperidinecarbonyl-N6-formyl-N6-hydroxy-L-lysyl-O-methyl-D-tyrosyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7

ST cyclic peptide retrohydroxamate zinc ligand prepn inhibitor histone deacetylase; antitumor potential cyclic peptide retrohydroxamate zinc ligand

IT Peptides, preparation
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; synthesis and histone deacetylase inhibitory activity of potential antitumor cyclic tetrapeptides containing retrohydroxamate as zinc ligand)

IT Antitumor agents
(synthesis and histone deacetylase inhibitory activity of potential antitumor cyclic tetrapeptides containing retrohydroxamate as zinc ligand)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis and histone deacetylase inhibitory activity of potential antitumor cyclic tetrapeptides containing retrohydroxamate as zinc ligand)

IT 727425-92-5P 727425-93-6P 727425-94-7P
727425-95-8P 727425-96-9P 727425-97-0P
727425-98-1P 727425-99-2P 727426-00-8P
727426-01-9P 727426-02-0P 727426-03-1P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and histone deacetylase inhibitory activity of potential antitumor cyclic tetrapeptides containing retrohydroxamate as zinc ligand)

IT 727426-05-3P 727426-06-4P
RL: BYP (Byproduct); PREP (Preparation)
(synthesis and histone deacetylase inhibitory

activity of potential antitumor cyclic tetrapeptides containing retrohydroxamate as zinc ligand)

IT 622-33-3, o Benzylhydroxylamine 2916-68-9, 2-(Trimethylsilyl)ethanol 4797-81-3 183991-46-0 221187-08-2 227185-30-0 669091-26-3 669091-27-4 669091-38-7 727426-40-6 727426-75-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and histone deacetylase inhibitory activity of potential antitumor cyclic tetrapeptides containing retrohydroxamate as zinc ligand)

IT 161264-15-9P 669091-40-1P 727426-04-2P 727426-07-5P 727426-08-6P 727426-09-7P 727426-10-0P 727426-11-1P 727426-12-2P 727426-13-3P 727426-14-4P 727426-15-5P 727426-16-6P 727426-17-7P 727426-18-8P 727426-19-9P 727426-20-2P 727426-21-3P 727426-22-4P 727426-23-5P 727426-24-6P 727426-25-7P 727426-26-8P 727426-27-9P 727426-28-0P 727426-29-1P 727426-30-4P 727426-31-5P 727426-32-6P 727426-33-7P 727426-34-8P 727426-35-9P 727426-36-0P 727426-37-1P 727426-38-2P 727426-39-3P 727426-41-7P 727426-42-8P 727426-43-9P 727426-44-0P 727426-45-1P 727426-46-2P 727426-47-3P 727426-48-4P 727426-49-5P 727426-50-8P 727426-51-9P 727426-52-0P 727426-53-1P 727426-54-2P 727426-55-3P 727426-56-4P 727426-57-5P 727426-58-6P 727426-59-7P 727426-60-0P 727426-61-1P 727426-62-2P 727426-63-3P 727426-64-4P 727426-65-5P 727426-66-6P 727426-67-7P 727426-68-8P 727426-69-9P 727426-70-2P 727426-71-3P 727426-72-4P 727426-73-5P 727426-74-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and histone deacetylase inhibitory activity of potential antitumor cyclic tetrapeptides containing retrohydroxamate as zinc ligand)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 18 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:28701 HCAPLUS Full-text
DOCUMENT NUMBER: 141:116594
TITLE: Design synthesis of SS-dimers and SS-hybrids based on Cyl-1 (cyclic tetrapeptide) as anti-cancer prodrugs
AUTHOR(S): Nishino, Norikazu; Okamura, Shinji; Ebisuzaki, Shutoku; Kato, Tamaki; Sumida, Yuko; Yoshida, Minoru
CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196, Japan
SOURCE: Peptides 2002, Proceedings of the European Peptide Symposium, 27th, Sorrento, Italy, Aug. 31-Sept. 6, 2002 (2002), 830-831. Editor(s): Benedetti, Ettore; Pedone, Carlo. Edizioni Ziino: Castellammare di Stabia, Italy.
CODEN: 69EYXG; ISBN: 88-900948-1-8
DOCUMENT TYPE: Conference
LANGUAGE: English

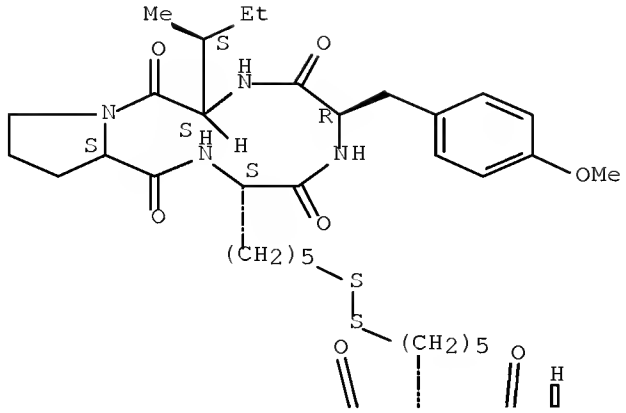
AB Design and synthesis of SS-dimers and SS-hybrids based on Cyl-1 (cyclic tetrapeptide) as anti-cancer prodrugs is described.

IT 591772-31-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of SS-dimers and SS-hybrids based on Cyl-1 as anticancer prodrugs)

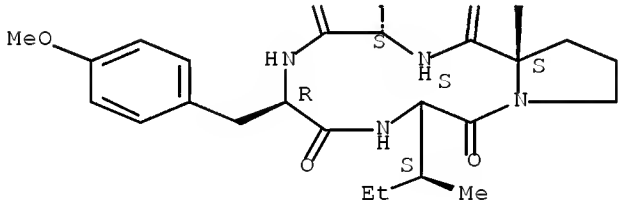
RN 591772-31-5 HCAPLUS
CN Cyclo[(2S)-2-amino-7-mercaptoheptanoyl-O-methyl-D-tyrosyl-L-isoleucyl-L-prolyl], bimol. (1→1')-disulfide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



CC 1-6 (Pharmacology)
Section cross-reference(s): 34, 63
IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(1; synthesis of SS-dimers and SS-hybrids based on Cyl-1 as anticancer prodrugs)
IT 591772-31-5 591772-81-5 591772-85-9
591772-85-9D, derivs. 591772-87-1 591772-89-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of SS-dimers and SS-hybrids based on Cyl-1 as anticancer prodrugs)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 19 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:957798 HCAPLUS Full-text
DOCUMENT NUMBER: 140:128676
TITLE: Cyclic Tetrapeptides Bearing a Sulfhydryl Group

Potently Inhibit Histone Deacetylases

AUTHOR(S): Nishino, Norikazu; Jose, Binoy; Okamura, Shinji; Ebisusaki, Shutoku; Kato, Tamaki; Sumida, Yuko; Yoshida, Minoru

CORPORATE SOURCE: Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, Wakamatsu, Kitakyushu, 808-0196, Japan

SOURCE: Organic Letters (2003), 5(26), 5079-5082
CODEN: ORLEF7; ISSN: 1523-7060

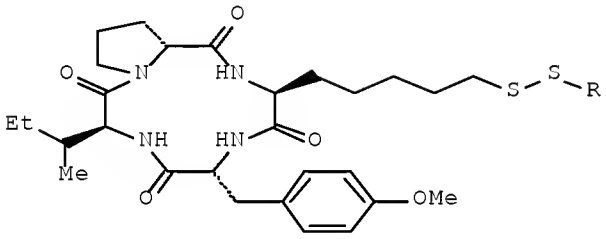
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 140:128676

GI



I

AB New inhibitors of histone deacetylase (HDAC) containing a sulfhydryl group, such as cyclic peptide I (R = H), were designed on the basis of the corresponding hydroxamic acid (CHAP31) and FK228. Disulfide dimers and hybrids of such cyclic peptides, I [R = 4-pyridyl, 2-pyridyl, CH2CH2OH, 3-(N,N-dimethylcarboxamido)-4-nitrophenyl, R = itself for the dimer], exhibited potent HDAC inhibitory activity in vivo with potential as anticancer prodrugs.

IT 591772-81-5P

RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

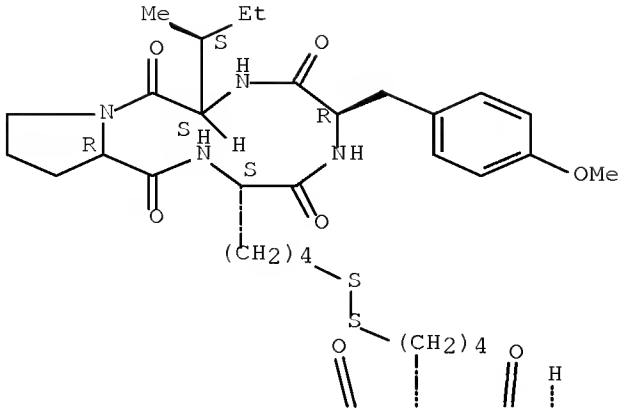
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

RN 591772-81-5 HCAPLUS

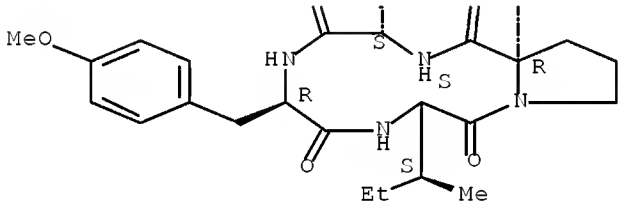
CN Cyclo(L-isoleucyl-D-prolyl-6-mercapto-L-norleucyl-O-methyl-D-tyrosyl), bimol. (3→3')-disulfide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7
ST sulfhydryl cyclic peptide prepn inhibitor histone deacetylase; anticancer prodrug disulfide bonded cyclic peptide
IT Peptides, preparation
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cyclic; preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors
of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)
IT Peptides, preparation
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(disulfide-containing; preparation of sulfhydryl-containing cyclic tetrapeptides as
inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)
IT Structure-activity relationship
(enzyme-inhibiting; preparation of sulfhydryl-containing cyclic tetrapeptides as
inhibitors of histone deacetylases, and their

disulfide-bonded peptides as potential anticancer prodrugs)

IT Antitumor agents
Neoplasm
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT Drug delivery systems
(prodrugs; preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 591772-81-5P 591772-87-1P 591772-89-3P
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 591772-31-5P 591772-43-9P 591772-45-1P
591772-91-7P 591772-93-9P 591772-97-3P
648929-41-3P 648929-43-5P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 58880-19-6, Trichostatin A
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 128517-07-7, FK228
RL: PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 591772-85-9P 591772-95-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 390745-19-4P 591773-10-3P 591773-11-4P
591773-12-5P 591773-13-6P 648929-42-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 60-24-2, 2-Mercaptoethanol 2127-03-9, 2,2'-Dithiodipyridine 2645-22-9, 4,4'-Dithiodipyridine 13139-16-7 53843-90-6 68856-96-2 350578-43-7 591772-17-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of

histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

IT 221187-05-9P 221187-06-0P 591772-49-5P 591772-59-7P 591772-65-5P 591772-67-7P 591772-69-9P 591772-75-7P 648929-44-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of sulfhydryl-containing cyclic tetrapeptides as inhibitors of histone deacetylases, and their disulfide-bonded peptides as potential anticancer prodrugs)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 20 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:678832 HCAPLUS Full-text

DOCUMENT NUMBER: 139:230998

TITLE: Preparation of cyclic peptides as histone deacetylase inhibitors

INVENTOR(S): Yoshida, Minoru; Nishino, Norikazu; Horinouchi, Sueharu

PATENT ASSIGNEE(S): Japan

SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070754	A1	20030828	WO 2003-JP1859	20030220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003211576	A1	20030909	AU 2003-211576	20030220
CN 1646558	A	20050727	CN 2003-808875	20030220
US 20050277583	A1	20051215	US 2005-505380	20050617
PRIORITY APPLN. INFO.:			JP 2002-44000 A	20020220
			WO 2003-JP1859 W	20030220

OTHER SOURCE(S): MARPAT 139:230998

GI

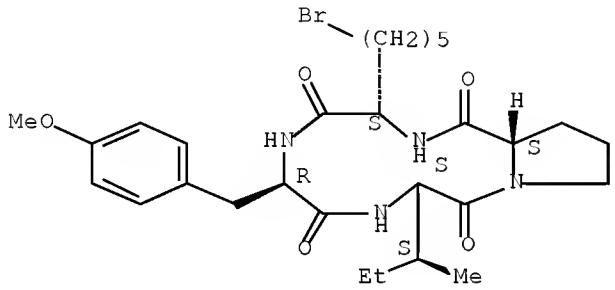
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. I [wherein R11, R21, R31, and R41 = independently H or Me; R22, R23, R32, R33, R42, and R43 = independently H, (un)substituted alkyl, or cycloalkyl, etc.; X = H, (un)substituted alkyl, or aryl, etc.; n = an integer] are prepared as histone deacetylase (HDAC) inhibitors for treating diseases caused by HDAC1 and HDAC4. For example, the compound II was prepared in a

multi-step synthesis in good yield. II showed IC50 of 61.1 nM and 36.2 nM against human HDAC1 and HDAC4, resp.

IT 591772-27-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of cyclic peptides as histone deacetylase inhibitors)
RN 591772-27-9 HCAPLUS
CN Cyclo[(2S)-2-amino-7-bromoheptanoyl-O-methyl-D-tyrosyl-L-isoleucyl-L-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IC ICM C07K005-12
ICS C12N009-99; A61K038-00; A61P017-00; A61P031-00; A61P035-00; A61P037-00; A61P043-00
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST cyclic peptide histone deacetylase inhibitor prepn human; HDAC inhibitor cyclic peptide prepn
IT Disease, animal
(HDAC1 or HDAC4 initiated; preparation of cyclic peptides as histone deacetylase inhibitors)
IT Apoptosis
Cell differentiation
(induction drug; preparation of cyclic peptides as histone deacetylase inhibitors)
IT Angiogenesis
(neovascularization, inhibitor; preparation of cyclic peptides as histone deacetylase inhibitors)
IT Anti-infective agents
Antitumor agents
Autoimmune disease
Human
Immunomodulators
Infection
Skin, disease
(preparation of cyclic peptides as histone deacetylase inhibitors)
IT Neoplasm
(transfer inhibitor; preparation of cyclic peptides as histone deacetylase inhibitors)
IT 591772-27-9P 591772-29-1P 591772-41-7P
591772-42-8P 591772-44-0P 591772-65-5P

591772-67-7P 591772-69-9P 591772-71-3P
591772-73-5P 591772-75-7P 591772-77-9P
591772-79-1P 591773-01-2P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of cyclic peptides as histone deacetylase inhibitors)

IT 591772-31-5P 591772-43-9P 591772-45-1P
591772-81-5P 591772-85-9P 591772-87-1P
591772-89-3P 591772-91-7P 591772-93-9P
591772-95-1P 591772-97-3P 591772-99-5P
591773-03-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of cyclic peptides as histone deacetylase inhibitors)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; preparation of cyclic peptides as histone deacetylase inhibitors)

IT 74257-99-1P 221187-05-9P 221187-06-0P 259222-06-5P 291312-95-3P
591772-17-7P 591772-18-8P 591772-19-9P 591772-22-4P 591772-23-5P
591772-24-6P 591772-26-8P 591772-34-8P 591772-36-0P 591772-39-3P
591772-47-3P 591772-49-5P 591772-51-9P 591772-53-1P 591772-56-4P
591772-59-7P 591772-61-1P 591772-64-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of cyclic peptides as histone deacetylase inhibitors)

IT 591773-07-8 591773-08-9 591773-09-0
591773-10-3 591773-11-4 591773-12-5
591773-13-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of cyclic peptides as histone deacetylase inhibitors)

IT 100-39-0, Benzyl bromide 100-51-6, Benzyl alcohol, reactions
2127-03-9, 2,2'-Dithiodipyridine 2645-22-9, 4,4'-Dithiodipyridine
2916-68-9, 2-(Trimethylsilyl)ethanol 6258-60-2, 4-Methoxybenzylmercaptan
13139-16-7 15761-39-4 24424-99-5, Di-tert-butyl dicarbonate
37784-17-1 68856-96-2 98265-80-6 152922-78-6 350578-43-7
591773-04-5 591773-05-6 591773-06-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclic peptides as histone deacetylase inhibitors)

IT 591772-20-2P 591772-21-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of cyclic peptides as histone deacetylase inhibitors)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 21 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:509378 HCAPLUS Full-text
DOCUMENT NUMBER: 140:52743
TITLE: Hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone

deacetylases

AUTHOR(S): Nishino, Norikazu; Tomizaki, Kin-ya; Tsukamoto, Makiko; Yoshikawa, Daisuke; Shinta, Ryuzo; Nishino, Hidekazu; Tanaka, Yuji; Kato, Tamaki; Komatsu, Yasuhiko; Nishiyama, Makoto; Furumai, Ryohei; Yoshida, Minoru

CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Engineering, Kyushu Institute of Technology, Tobata, Kitakyushu, 804-8550, Japan

SOURCE: Peptides 2000, Proceedings of the European Peptide Symposium, 26th, Montpellier, France, Sept. 10-15, 2000 (2001), Meeting Date 2000, 41-42. Editor(s): Martinez, Jean; Fehrentz, Jean-Alain. Editions EDK: Paris, Fr.
CODEN: 69EDWK; ISBN: 2-84254-048-4

DOCUMENT TYPE: Conference

LANGUAGE: English

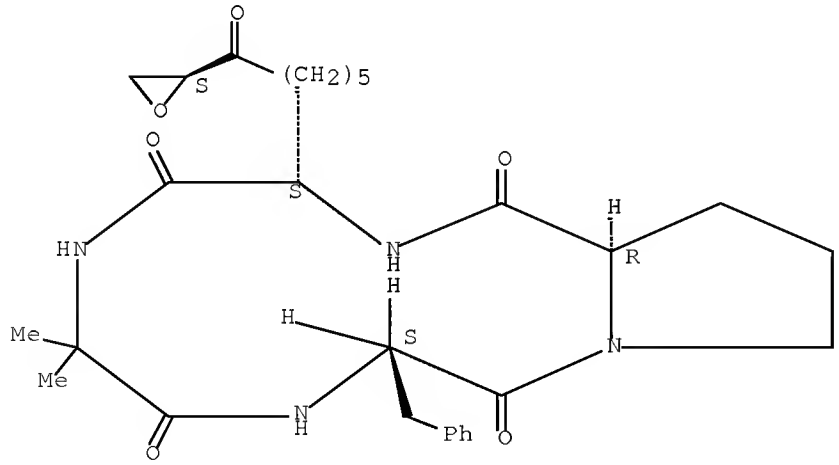
AB Cyclic hydroxamic acid-containing peptides (CHAPs)were designed and synthesized based on sequences of naturally occurring peptides. The CHAPs were examined for activities in histone deacetylase inhibition and MHC class-I expression.

IT 53342-16-8, Chlamydocin
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

RN 53342-16-8 HCAPLUS

CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 1-3 (Pharmacology)
Section cross-reference(s): 7, 34

ST hydroxamate analog tetrapeptide prepn histone deacetylase inhibiting immunomodulator structure; aminosuberate benzyl ester cyclicpeptide design histone deacetylase inhibition kinetics

IT Hydroxamic acids

RL: PRP (Properties); RCT (Reactant); RACT (Reactant or reagent)
(cyclic; hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

IT Structure-activity relationship
(histone deacetylase inhibiting; hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

IT Melanoma
(hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

IT Structure-activity relationship
(immunomodulating; hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

IT Enzyme kinetics
(of inhibition; hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

IT Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetrapeptides; hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

IT 53342-16-8, Chlamydocin 83209-65-8, HC-toxin
86402-37-1, WF-3161 90965-62-1, Cyl-1
133155-89-2, Trapoxin a
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

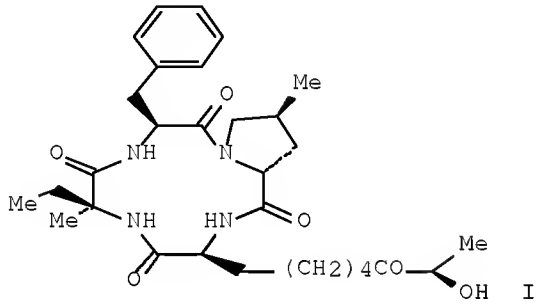
IT 221186-39-6P 221186-42-1P 221186-43-2P
221186-45-4P 221186-46-5P 221186-60-3P
221186-64-7P 221186-66-9P 221186-70-5P
331836-53-4P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; hydroxamic acid analogs of naturally-occurring cyclic tetrapeptides, trapoxin, WF-3161, Cyl-1, HC-toxin and chlamydocin inhibit histone deacetylases)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 22 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:193513 HCAPLUS Full-text
DOCUMENT NUMBER: 139:273315
TITLE: FR235222, a fungal metabolite, is a novel immunosuppressant that inhibits mammalian histone deacetylase. III. Structure determination

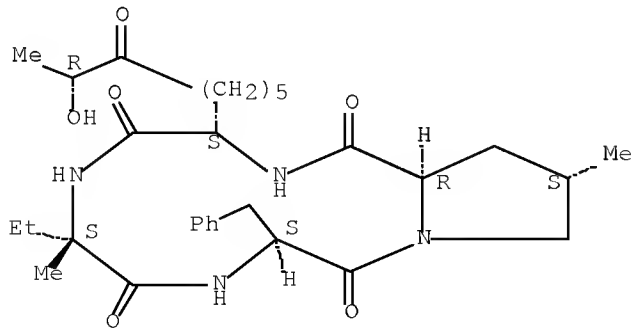
AUTHOR(S): Mori, Hiroaki; Urano, Yasuharu; Kinoshita, Takayoshi; Yoshimura, Seiji; Takase, Shigehiro; Hino, Motohiro
CORPORATE SOURCE: Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Tsukuba, 300-2698, Japan
SOURCE: Journal of Antibiotics (2003), 56(2), 181-185
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The structure determination of immunosuppressant FR235222 (I), including its absolute stereochem., is presented. I is a macrocyclic compound composed of L-Phe and 3 unique amino acids, i.e. 4-methylproline, isovaline, and 2-amino-8-oxo-p-hydroxydecanoic acid.
IT 264259-89-4, FR 235222
RL: PRP (Properties)
(structure determination of the histone deacetylase -inhibiting immunosuppressant FR235222)
RN 264259-89-4 HCAPLUS
CN Cyclo[(2S,9R)-2-amino-9-hydroxy-8-oxodecanoyl-L-isovalyl-L-phenylalanyl-(4S)-4-methyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

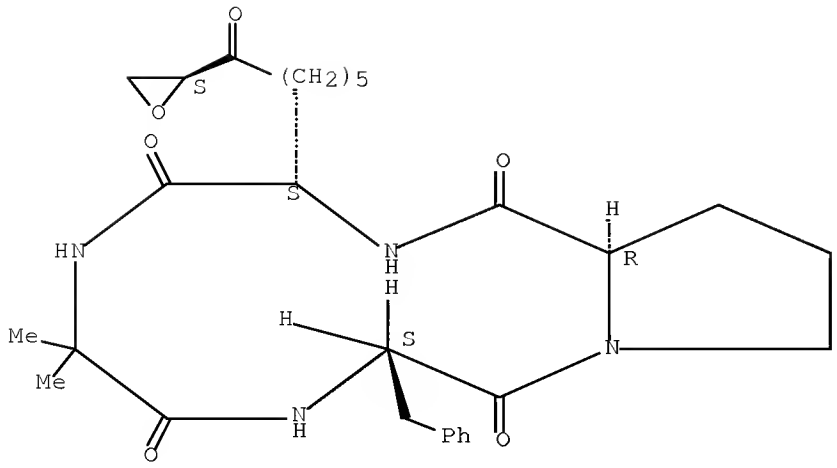


CC 10-1 (Microbial, Algal, and Fungal Biochemistry)
Section cross-reference(s): 34
IT 264259-89-4, FR 235222

RL: PRP (Properties)
(structure determination of the histone deacetylase -inhibiting immunosuppressant FR235222)
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 23 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:692467 HCAPLUS Full-text
DOCUMENT NUMBER: 138:385700
TITLE: Design of analogs of trapoxin, Cyl-1, and chlamydocin for MHC class-I molecule up-regulation
AUTHOR(S): Nishino, Norikazu; Kato, Tamaki; Komatsu, Yasuhiko; Yoshida, Minoru
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Engineering, Kyushu Institute of Technology, Kitakyushu, 804-8550, Japan
SOURCE: Peptides: The Wave of the Future, Proceedings of the Second International and the Seventeenth American Peptide Symposium, San Diego, CA, United States, June 9-14, 2001 (2001), 528-529. Editor(s): Lebl, Michal; Houghten, Richard A. American Peptide Society: San Diego, Calif.
CODEN: 69DBAL; ISBN: 0-9715560-0-8
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report. Stereoisomers of trapoxin hydroxamic acid analogs were synthesized and subjected to histone deacetylase (HDAC) inhibition and major histocompatibility complex (MHC) class-I mol. up-regulating assays. The stereoisomers of trapoxin B analogs having LDLD (7), LDLL (3) and retro-enantio DLDL (9) configurations inhibited HDAC with almost the same high potency. The isomer 7 showed nearly 200 times higher activity than the isomer 3 and 25 times higher activity than the retro-enantio analog 9 in the MHC assay. High performance liquid chromatog. retention times indicate that the hydrophobicity of the cyclic tetrapeptide framework is also necessary for MHC activity.
IT 53342-16-8DP, Chlamydocin, analogs
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(analogs of trapoxin, Cyl-1, and chlamydocin for MHC class-I mol. up-regulation)
RN 53342-16-8 HCAPLUS
CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7
ST trapoxin hydroxamic acid analog prepn histone deacetylase assay symposium; cyl1 analog prepn histone deacetylase assay symposium; chlamydocin analog histone deacetylase assay symposium
IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (analogs of trapoxin, Cyl-1, and chlamydocin for MHC class-I mol. up-regulation)
IT 53342-16-8DP, Chlamydocin, analogs 90965-62-1DP, Cyl-1, analogs 133155-90-5DP, Trapoxin b, hydroxamic acid analogs 221186-39-6P 221186-56-7P 221186-58-9P 221186-62-5P 527705-77-7P 527705-82-4P 527705-87-9P 527705-90-4P 527705-94-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (analogs of trapoxin, Cyl-1, and chlamydocin for MHC class-I mol. up-regulation)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

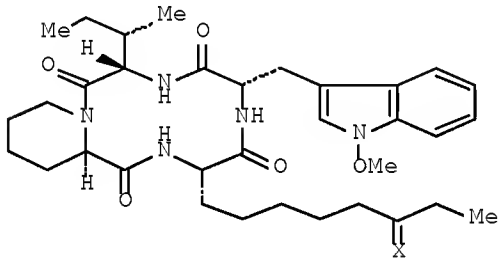
L17 ANSWER 24 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:504791 HCAPLUS Full-text
DOCUMENT NUMBER: 137:79231
TITLE: Preparation and formulation of apicidin derivatives for use as antitumor agents
INVENTOR(S): Lee, Hyang Woo; Jung, Young Hoon; Han, Jeung Whan; Lee, Seok Yong; Lee, Yin Won; Lee, Hoi Young; Zee, Ok Pyo
PATENT ASSIGNEE(S): S. Korea
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002051846	A1	20020704	WO 2001-KR2228		20011221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
KR 2002051859	A	20020629	KR 2001-82346		20011221
AU 2002216464	A1	20020708	AU 2002-216464		20011221
JP 2004516328	T	20040603	JP 2002-552941		20011221
US 20040014647	A1	20040122	US 2003-600392		20030620
US 6831061	B2	20041214			
PRIORITY APPLN. INFO.:			KR 2000-80180	A	20001222
			WO 2001-KR2228	W	20011221

OTHER SOURCE(S): CASREACT 137:79231; MARPAT 137:79231

GI



I

AB Apicidin derivs. I [X = semicarbazone, thiosemicarbazone, hydrazone, tert-butylhydrazone, phenylhydrazone, 2,4-dinitrophenylhydrazone, 4-methoxyphenylhydrazone, 3-methoxyphenylhydrazone, 4-nitrophenylhydrazone, benzylhydrazone, methanesulfonylhydrazone, benzenesulfonylhydrazone, 4-methylbenzenezulfonylhydrazone, benzoylhydrazone, 4-nitrobenzoylhyrazone, carbohydrazone, benzyloxime, acetoxime] were prepared for pharmaceutical use in the treatment of cancer. Thus, apicidin Ia I (X = O), which was obtained via a fermentation process, was reacted with semicarbazide hydrochloride using Et3N in methanol to give apicidin Ia semicarbazone I (X = NNHCONH2) in 85.3% yield. The prepared apicidin derivs. were tested for inhibition of histone deacetylase and growth of cancer cells.

IT 322000-66-8P

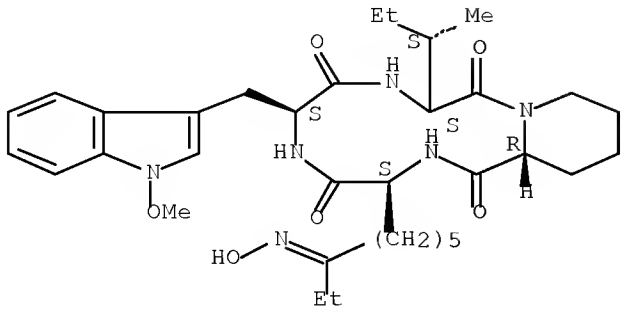
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation and formulation of apicidin derivs. for use as antitumor agents)

RN 322000-66-8 HCAPLUS

CN Cyclo[(2S)-2-amino-8-(hydroxyimino)decanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

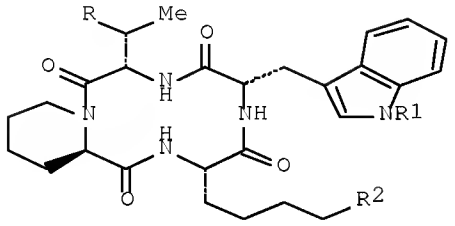
Absolute stereochemistry.
Double bond geometry unknown.



IC ICM C07D487-04
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 16, 63
IT 322000-66-8P
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation and formulation of apicidin derivs. for use as antitumor agents)
IT 322000-67-9P 439859-08-2P, Apicidin Ia semicarbazone
439859-09-3P 439859-10-6P 439859-11-7P
439859-12-8P 439859-13-9P 439859-14-0P
439859-15-1P 439859-16-2P 439859-17-3P
439859-18-4P 439859-19-5P 439859-20-8P
439859-21-9P 439859-22-0P 439859-23-1P
439859-24-2P
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and formulation of apicidin derivs. for use as antitumor agents)
IT 183506-66-3P, Apicidin Ia
RL: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and formulation of apicidin derivs. for use as antitumor agents)
IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation and formulation of apicidin derivs. for use as antitumor agents)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 25 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:34206 HCAPLUS Full-text
DOCUMENT NUMBER: 136:232540
TITLE: Structure and Chemistry of Apicidins, a Class of Novel Cyclic Tetrapeptides without a Terminal α-Keto Epoxide as Inhibitors of Histone Deacetylase with Potent Antiprotozoal Activities

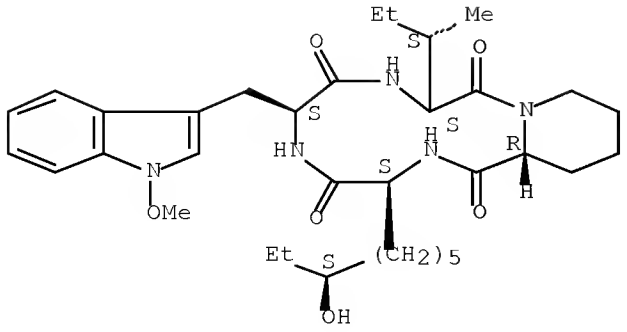
AUTHOR(S): Singh, Sheo B.; Zink, Deborah L.; Liesch, Jerrold M.; Mosley, Ralph T.; Dombrowski, Anne W.; Bills, Gerald F.; Darkin-Rattray, Sandra J.; Schmatz, Dennis M.; Goetz, Michael A.
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Organic Chemistry (2002), 67(3), 815-825
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:232540
GI



I

AB Apicidins I [R = Et, R1 = OMe, R2 = CH2COEt; R = Et, R1 = H, R2 = CH2COEt; R = Me, R1 = OMe, R2 = CH2COEt; R = Et, R1 = OMe, R2 = CH2COCH(OH)Me; R = Et, R1 = OMe, R2 = CH2CH(S-OH)Et; R = Et, R1 = OMe, R2 = CH2CH2CH(OH)Me] are a class of cyclic tetrapeptides that do not contain the classical electrophilic α-keto epoxide and yet are potent (nM) inhibitors of histone deacetylase and antiprotozoal agents. I showed broad-spectrum activities against the apicomplexan family of protozoa including Plasmodium sp (malarial parasite), Toxoplasma gondii, Cryptosporidium sp., and Eimeria sp. These cyclic peptides contain a β-turn amino acid (R)-Pip or (R)-Pro, (S)-N-methoxytryptophan, (S)-Ile or (S)-Val, and either (S)-2-amino-8-oxodecanoic acid or a modified (S)-2-amino-8-oxodecanoic acid. The isolation and structure elucidation of new apicidins from two Fusarium species, temperature-dependent NMR studies of apicidin, NMR and mol. modeling based conformation of the 12-membered macrocyclic ring, and selected chemical modifications of apicidin have been detailed in this paper. The cyclic nature of the peptide, the C-8 keto group, and the tryptophan are all critical for the biol. activity.
IT 177562-78-6, Apicidin D 2
RL: NPO (Natural product occurrence); PAC (Pharmacological activity); BIOL (Biological study); OCCU (Occurrence)
(isolation, structure elucidation, chemical and biol. activity of novel cyclic tetrapeptide apicidins as inhibitors of histone deacetylase with potent antiprotozoal activities)
RN 177562-78-6 HCAPLUS
CN Cyclo[(2S,8S)-2-amino-8-hydroxydecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7, 16

ST apicidin cyclic tetrapeptide isolation structure chem antiprotozoal activity; histone deacetylase inhibitory activity
apicidin deriv

IT Peptides, reactions
RL: NPO (Natural product occurrence); PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); OCCU (Occurrence); RACT (Reactant or reagent)
(cyclic, tetra-; isolation, structure elucidation, chemical and biol. activity of novel cyclic tetrapeptide apicidins as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT Antimalarials
Conformation
Molecular structure determination methods
Protozoacides
(isolation, structure elucidation, chemical and biol. activity of novel cyclic tetrapeptide apicidins as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT Natural products
RL: NPO (Natural product occurrence); PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); OCCU (Occurrence); RACT (Reactant or reagent)
(isolation, structure elucidation, chemical and biol. activity of novel cyclic tetrapeptide apicidins as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT 177562-78-6, Apicidin D 2 183506-67-4
189337-29-9 189337-30-2, Apicidin D 1
366448-28-4
RL: NPO (Natural product occurrence); PAC (Pharmacological activity); BIOL (Biological study); OCCU (Occurrence)
(isolation, structure elucidation, chemical and biol. activity of novel cyclic tetrapeptide apicidins as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT 177562-80-0, Apicidin D 3 183506-66-3
RL: NPO (Natural product occurrence); PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); OCCU (Occurrence); RACT (Reactant or reagent)
(isolation, structure elucidation, chemical and biol. activity of novel cyclic tetrapeptide apicidins as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(preparation and biol. activity of apicidin derivs. as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT 314058-15-6P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(preparation and biol. activity of apicidin derivs. as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT 314058-18-9P 322000-67-9P 322000-72-6P 403501-69-9P 403501-70-2P 403501-71-3P 403501-72-4P 403501-73-5P 403501-74-6P 403501-75-7P 403501-76-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation and biol. activity of apicidin derivs. as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT 3966-32-3 26164-26-1

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation and biol. activity of apicidin derivs. as inhibitors of histone deacetylase with potent antiprotozoal activities)

IT 366001-35-6P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation and biol. activity of apicidin derivs. as inhibitors of histone deacetylase with potent antiprotozoal activities)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 26 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2000:818492 HCAPLUS Full-text

DOCUMENT NUMBER: 134:125542

TITLE: Synthesis of Apicidin-Derived Quinolone Derivatives: Parasite-Selective Histone Deacetylase Inhibitors and Antiproliferative Agents

AUTHOR(S): Meinke, Peter T.; Colletti, Steven L.; Doss, George; Myers, Robert W.; Gurnett, Anne M.; Dulski, Paula M.; Darkin-Rattray, Sandra J.; Allocco, John J.; Galuska, Stefan; Schmatz, Dennis M.; Wyvratt, Matthew J.; Fisher, Michael H.

CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065-0900, USA

SOURCE: Journal of Medicinal Chemistry (2000), 43(25), 4919-4922

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 134:125542

AB Apicidin's indole was efficiently converted into a series of N-substituted quinolone derivs. by indole N-alkylation followed by a two-step, one-pot, ozonolysis/aldol condensation protocol. The new quinolones exhibited good parasite selectivity and potency both at the level of their mol. target, histone deacetylase, and in their whole cell antiproliferative activity in vitro.

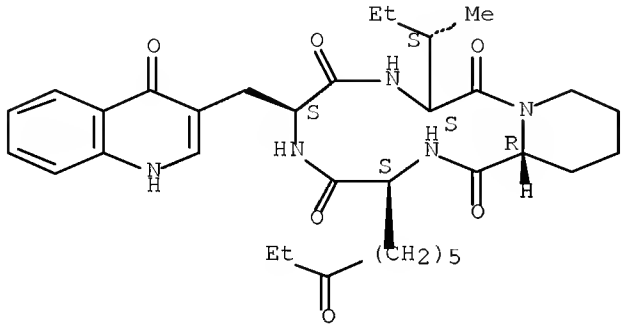
IT 321798-50-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

RN 321798-50-9 HCAPLUS

CN Cyclo[3-(1,4-dihydro-4-oxo-3-quinolinyl)-L-alanyl-L-isoleucyl-(2R)-2-piperidinecarbonyl-(2S)-2-amino-8-oxodecanoyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 1-3 (Pharmacology)
Section cross-reference(s): 34

ST apicidin histone deacetylase inhibitor quinolones prepn

IT Structure-activity relationship
(antiproliferative; synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

IT Structure-activity relationship
(enzyme-inhibiting, histone deacetylase-inhibiting; synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

IT Antibiotics
(quinolone; synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

IT Eimeria tenella
Malaria
Plasmodium falciparum
Protozoacides
(synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

IT 13721-01-2D, derivs., antibiotics
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(quinolone antibiotics; synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

IT 321798-50-9P 321798-56-5P 321798-61-2P
321798-68-9P 321798-73-6P 321798-81-6P

321798-87-2P 321798-93-0P 321798-98-5P
321799-04-6P 321799-09-1P 321799-14-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

IT 183506-66-3D, quinoline derivs. 183506-67-4, Apicidin a
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

IT 321798-41-8P
RL: PNU (Preparation, unclassified); PREP (Preparation)
(synthesis of apicidin-derived quinolone derivs. as parasite-selective histone deacetylase inhibitors and antiproliferative agents)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 27 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:805815 HCAPLUS Full-text
DOCUMENT NUMBER: 134:56953
TITLE: Design and synthesis of histone deacetylase inhibitors: the development of apicidin transition state analogs
AUTHOR(S): Colletti, Steven L.; Myers, Robert W.; Darkin-Rattray, Sandra J.; Schmatz, Dennis M.; Fisher, Michael H.; Wyvratt, Matthew J.; Meinke, Peter T.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, Merck and Co., Inc., Rahway, NJ, 07065, USA
SOURCE: Tetrahedron Letters (2000), 41(41), 7837-7841
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:56953

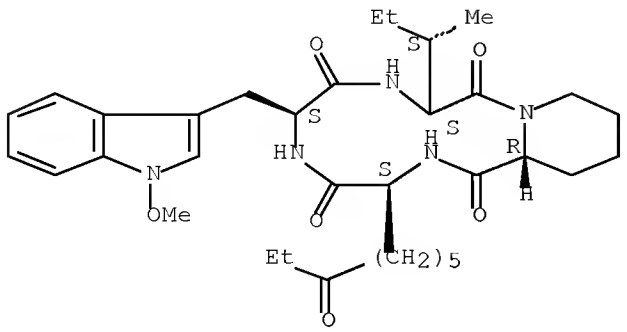
AB A four step degradation of the C8 Et ketone of apicidin provided a route to the C6 aldehyde intermediate and several mechanism-based transition state inhibitors of histone deacetylase. The compds. generated herein delineate the significance of apicidin's side chain, highlighted by the high affinity C8 aldehyde and C8-keto-9,10-epoxide analogs of apicidin.

IT 183506-66-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)

RN 183506-66-3 HCAPLUS
CN Cyclo[(2S)-2-amino-8-oxodecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-(2R)-2-

piperidinecarbonyl] (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

ST apicidin peptide transition state analog prepn histone deacetylase inhibitor; ethylketone apicidin side chain degrdn; ketoepoxide apicidin prepn antiprotozoal; aldehyde apicidin prepn structure activity histone deacetylase inhibitor

IT Structure-activity relationship
(histone deacetylase binding affinity; preparation of apicidin transition state analogs as histone deacetylase inhibitors)

IT Protozoacides
Transition state structure
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)

IT 183506-66-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)

IT 314058-25-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)

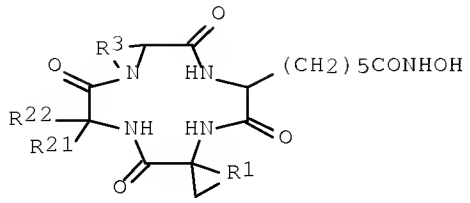
IT 312956-88-0P 312956-97-1P 314058-18-9P
314058-19-0P 314058-20-3P 314058-23-6P
314058-24-7P 314058-26-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)

IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)
IT 79-42-5, Thiolactic acid 2136-75-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)
IT 314058-15-6P 314058-17-8P 314058-21-4P
314058-22-5P 314058-28-1P 314058-29-2P
314058-31-6P 314058-32-7P 314058-33-8P
314058-34-9P 314058-35-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)
IT 314058-27-0P 314058-30-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of apicidin transition state analogs as histone deacetylase inhibitors)
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 28 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:628159 HCAPLUS Full-text
DOCUMENT NUMBER: 133:223052
TITLE: Preparation of novel cyclic tetrapeptide derivatives and use thereof as drugs
INVENTOR(S): Nishino, Norikazu; Yoshida, Minoru; Horinouchi, Sueharu; Komatsu, Yasuhiko
PATENT ASSIGNEE(S): Japan Energy Corporation, Japan
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000052033	A1	20000908	WO 2000-JP1141	20000228
W: AU, CA, NO, NZ, US, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 2000256397	A	20000919	JP 1999-53851	19990302
CA 2362817	A1	20000908	CA 2000-2362817	20000228
NZ 513983	A	20010928	NZ 2000-513983	20000228
EP 1174438	A1	20020123	EP 2000-905381	20000228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO 2001004225	A	20011017	NO 2001-4225	20010831
US 20020120099	A1	20020829	US 2001-945237	20010831
US 6825317	B2	20041130		
ZA 2001007320	A	20020904	ZA 2001-7320	20010904
PRIORITY APPLN. INFO.:			JP 1999-53851 A	19990302
			WO 2000-JP1141 W	20000228

OTHER SOURCE(S): MARPAT 133:223052
GI



I

AB Cyclic tetrapeptide derivs. represented by general formula (I) or pharmaceutically acceptable salts thereof (wherein R21 and R22 are each independently hydrogen, linear C1-6 alkyl to which a nonarom. cycloalkyl group or an optionally substituted aromatic ring may be bonded, or branched C3-6 alkyl to which a nonarom. cycloalkyl group or an optionally substituted aromatic ring may be bonded; and R1 and R3 are each independently linear C1-5 alkylene which may have a C1-6 side chain, and the side chain may form a fused ring structure on the alkylene chain) are prepared Also claimed are histone deacetylase inhibitors, MHC class I mol. expression promoters and anticancer drug compns., containing as the active ingredient the above tetrapeptide derivs. or pharmaceutically acceptable salts thereof. Thus, cyclo(-L-Asu(NHOH)-2Ain-L-Phe-D-Pro-) (2Ain = 2-aminoindane-2-carboxylic acid residue), which was prepared by the solution phase method, in vitro at 1.29 nM doubled the amount of MHC class I mol. expressed on the surface of B16/BL6 cells and also showed IC50 of 0.980 nM against histone deacetylase.

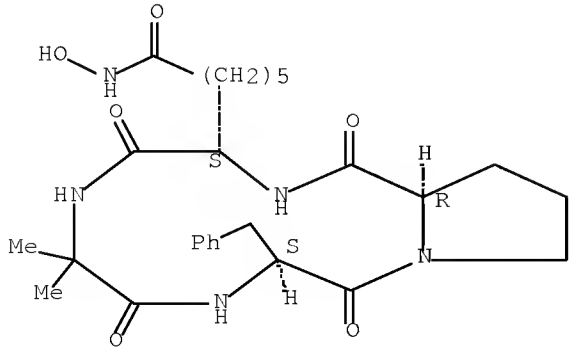
IT 221186-45-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors, MHC class I mol. expression promoters, and anticancer agents)

RN 221186-45-4 HCAPLUS

CN Cyclo[2-methylalanyl-L-phenylalanyl-D-prolyl-(2S)-2-amino-8-(hydroxyamino)-8-oxooctanoyl] (CA INDEX NAME)

Absolute stereochemistry.



IC ICM C07K005-12
ICS A61K038-12
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST cyclic tetrapeptide prepn anticancer; histone deacetylase inhibitor cyclic tetrapeptide prepn; MHC I mol expression promotor cyclic tetrapeptide prepn
IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex); preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors, MHC class I mol. expression promoters, and anticancer agents)
IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors, MHC class I mol. expression promoters, and anticancer agents)
IT Antitumor agents
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors, MHC class I mol. expression promoters, and anticancer agents)
IT 221186-45-4P 291312-79-3P 291312-80-6P
291312-81-7P 291312-82-8P 291312-83-9P
291312-84-0P 291312-85-1P 291312-86-2P
291312-88-4P 291312-90-8P 291312-92-0P
291313-19-4P 291313-20-7P 291313-22-9P
291313-23-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors, MHC class I mol. expression promoters, and anticancer agents)
IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors, MHC class I mol. expression promoters, and anticancer agents)
IT 1161-13-3 13139-16-7 15030-72-5 27473-62-7, 2-Aminoindan-2-carboxylic acid 38068-77-8 90071-62-8, D-Proline tert-butyl ester 127095-92-5, Boc-D-Cha-OH 174784-95-3, Boc-Asu(OBzl)-OH 221187-27-5, Boc-Asu(OBzl)-OTmse
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors, MHC class I mol. expression promoters, and anticancer agents)
IT 162757-06-4P 221186-79-4P 221186-91-0P 221186-92-1P
286436-68-8P 291312-77-1P 291312-78-2P 291312-95-3P
291312-97-5P 291313-00-3P 291313-03-6P 291313-05-8P 291313-10-5P
291313-13-8P 291313-16-1P 291313-18-3P
291313-21-8P 291313-24-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors, MHC class I mol. expression promoters,

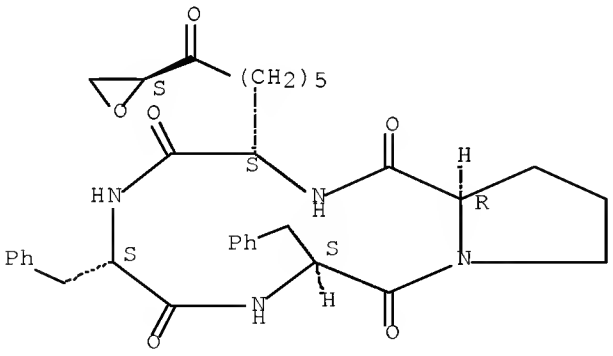
and anticancer agents)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 29 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:288753 HCAPLUS Full-text
DOCUMENT NUMBER: 133:164306
TITLE: Cyclic tetrapeptide hydroxamic acids related to trapoxin B inhibit histone deacetylase
AUTHOR(S): Nishino, Norikazu; Tomizaki, Kin-Ya; Mimoto, Tsutomu; Komatsu, Yasuhiko; Kim, Young Bae; Yoshida, Minoru
CORPORATE SOURCE: Institute for Fundamental Research of Organic Chemistry, Kyushu University, Fukuoka, 812-8581, Japan
SOURCE: Peptides 1998, Proceedings of the European Peptide Symposium, 25th, Budapest, Aug. 30-Sept. 4, 1998 (1999), Meeting Date 1998, 832-833. Editor(s): Bajusz, Sandor; Hudecz, Ferenc. Akademiai Kiado: Budapest, Hung.
CODEN: 68WKAY
DOCUMENT TYPE: Conference
LANGUAGE: English

AB A symposium report. Trapoxin B analogs, cyclic tetrapeptides containing α-aminosuberyl, α-aminoazelayl, and α-aminopimelyl ω-hydroxamic acids, were prepared and tested for inhibition of histone deacetylase.

IT 133155-90-5DP, Trapoxin B, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of trapoxin B-related cyclic tetrapeptide hydroxamic acids as histone deacetylase inhibitors)
RN 133155-90-5 HCAPLUS
CN Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-L-phenylalanyl-L-phenylalanyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7
ST cyclotetrapeptide hydroxamic acid prepn histone deacetylase inhibitor symposium; peptide cyclic trapoxin B analog prepn symposium
IT Hydroxamic acids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(alkanedioic hydroxyamides; preparation of trapoxin B-related cyclic tetrapeptide hydroxamic acids as histone deacetylase inhibitors)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cyclic; preparation of trapoxin B-related cyclic tetrapeptide hydroxamic acids as histone deacetylase inhibitors)

IT Structure-activity relationship
(histone deacetylase inhibitory; preparation of trapoxin B-related cyclic tetrapeptide hydroxamic acids as histone deacetylase inhibitors)

IT 133155-90-5DP, Trapoxin B, analogs 221186-39-6P 221186-42-1P 221186-43-2P 221186-56-7P 221186-58-9P 221186-59-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of trapoxin B-related cyclic tetrapeptide hydroxamic acids as histone deacetylase inhibitors)

IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of trapoxin B-related cyclic tetrapeptide hydroxamic acids as histone deacetylase inhibitors)

IT 221186-82-9 256520-77-1 256520-78-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of trapoxin B-related cyclic tetrapeptide hydroxamic acids as histone deacetylase inhibitors)

IT 221187-02-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of trapoxin B-related cyclic tetrapeptide hydroxamic acids as histone deacetylase inhibitors)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 30 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:683498 HCAPLUS Full-text
DOCUMENT NUMBER: 132:196
TITLE: Inhibitors of histone deacetylase suppress the growth of MCF-7 breast cancer cells
AUTHOR(S): Schmidt, Kathrin; Gust, Ronald; Jung, Manfred
CORPORATE SOURCE: Institut Pharmazie, Abteilung Pharmazeutische Chemie, Freie Univ. Berlin, Berlin, D-14195, Germany
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (1999), 332(10), 353-357
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inhibitors of histone deacetylase are attracting increasing interest due to their influence on transcription, differentiation, and apoptosis. Two synthetic inhibitors, (S)-MeO2CH(CH2Ph)NHCO(CH2)6CONHOH (I) and 4-Me2NC6H4CONH(CH2)6CONHOH (II) of histone deacetylase and the natural product inhibitor trichostatin A were studied for their ability to suppress the growth of MCF-7 breast cancer cells. Complete and improved synthetic procedures are presented. The compds. show a dose-independent inhibition of growth with

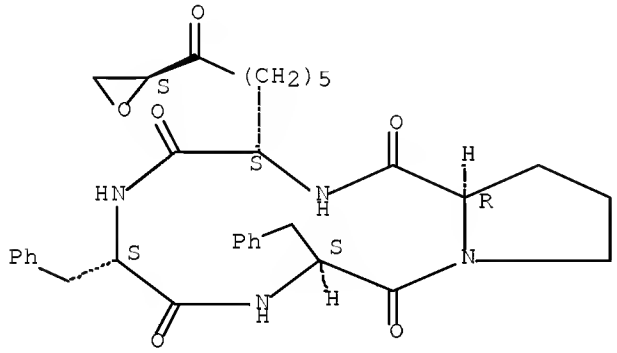
activities in the low micro- and nanomolar range. Trichostatin shows cytocidal effects at 100 nM and still has activity comparable to cisplatin (0.5 μM) at 10 nM. Whereas I has cytocidal activity at 10 μM, II shows a maximum of 40% growth-suppression at that concentration

IT 133155-90-5P, Trapoxin B
RL: BSU (Biological study, unclassified); PNU (Preparation, unclassified); BIOL (Biological study); PREP (Preparation)
(preparation of analog inhibitor of histone deacetylase suppressing growth of breast cancer)

RN 133155-90-5 HCAPLUS

CN Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-L-phenylalanyl-L-phenylalanyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 1-6 (Pharmacology)
Section cross-reference(s): 26, 34

IT 193550-93-5P 193551-00-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(inhibitor of histone deacetylase suppressing growth of breast cancer)

IT 58880-19-6P, Trichostatin A 133155-90-5P, Trapoxin B
RL: BSU (Biological study, unclassified); PNU (Preparation, unclassified); BIOL (Biological study); PREP (Preparation)
(preparation of analog inhibitor of histone deacetylase suppressing growth of breast cancer)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 31 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:353258 HCAPLUS Full-text
DOCUMENT NUMBER: 131:130254
TITLE: Synthesis of cyclic tetrapeptides containing non-natural imino acids
AUTHOR(S): Nishino, Hidekazu; Tomizaki, Kin-Ya; Kato, Tamaki; Nishino, Norikazu; Yoshida, Minoru; Komatsu, Yasuhiko
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Engineering, Kyushu Institute of Technology, Kitakyushu, 804-8550, Japan
SOURCE: Peptide Science (1999), Volume Date 1998, 35th, 189-192

CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Protein Research Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English

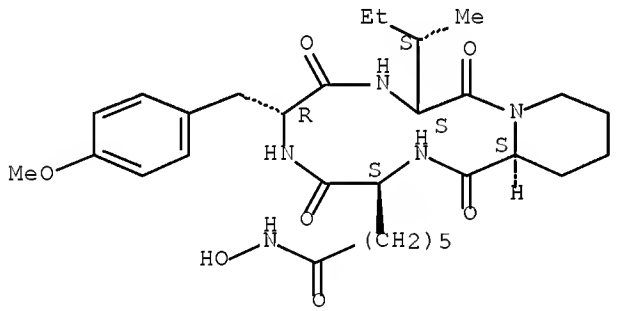
AB A symposium report. Cyl-2, WF-3161, and trapoxin A are inhibitors of the root growth of lettuce seedlings, cell growth in mouse P-388 leukemia cells, and mammalian histone deacetylase, resp. Unique amino acids (2S,9S)-2-amino-8-oxo-9,10-epoxydecanoic acid (L-Aoe) and pipecolic acid (Pip) are found within these cyclic tetrapeptide inhibitors : cyclo[L-Aoe-D-Tyr(Me)-L-Ile-L-Pip] (Cyl-2), cyclo(L-Aoe-D-Phe-L-Leu-L-Pip) (WF-3161), and cyclo(L-Aoe-L-Phe-L-Phe-D-Pip) (Trapoxin A). In order to study the effects of Pip on the inhibitory activity of these peptides toward histone deacetylase, the authors replaced it with various imino acids, such as 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic), hexamethyleneimine carboxylic acid (6Mic), and heptamethyleneimine carboxylic acid (7Mic), to obtain cyclo[L-Asu(NHOH)-D-Tyr(Me)-L-Ile-Xaa] (Xaa = Tic, 6Mic, 7Mic).

IT 221186-66-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of imino acid-containing cyclic tetrapeptides as inhibitors of histone deacetylase)

RN 221186-66-9 HCAPLUS

CN Cyclo[(2S)-2-amino-8-(hydroxyamino)-8-oxooctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-(2S)-2-piperidinecarbonyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7

ST imino acid substituted Cyl2 prepn symposium; Pip contg cyclic tetrapeptide inhibitor histone deacetylase symposium

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cyclic; synthesis of imino acid-containing cyclic tetrapeptides as inhibitors of histone deacetylase)

IT Carboxylic acids, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(imino; synthesis of imino acid-containing cyclic tetrapeptides as inhibitors of histone deacetylase)

IT 221186-66-9P 221186-67-0P 221186-68-1P
221186-69-2P 234112-50-6P 234112-51-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of imino acid-containing cyclic tetrapeptides as inhibitors of histone deacetylase)

IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synthesis of imino acid-containing cyclic tetrapeptides as inhibitors of histone deacetylase)

IT 42002-26-6, Cyl-2 86402-37-1, WF-3161
133155-89-2, Trapoxin A
RL: MSC (Miscellaneous)
(synthesis of imino acid-containing cyclic tetrapeptides as inhibitors of histone deacetylase)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

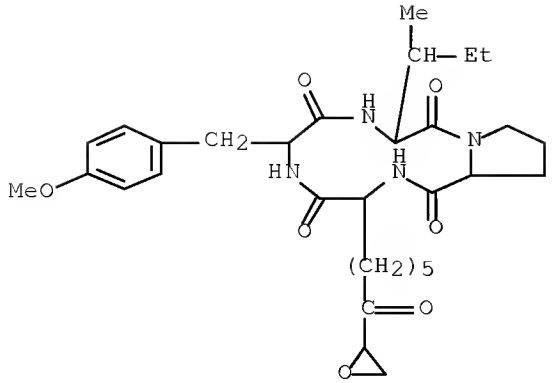
L17 ANSWER 32 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:353257 HCAPLUS Full-text
DOCUMENT NUMBER: 131:130253
TITLE: Synthesis and activity of Cyl-1 analogs having hydroxamic acid at side chain
AUTHOR(S): Tsukamoto, Makiko; Tomizaki, Kin-Ya; Kato, Tamaki; Nishino, Norikazu; Yoshida, Minoru; Komatsu, Yasuhiko
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Engineering, Kyushu Institute of Technology, Kitakyushu, 804-8550, Japan
SOURCE: Peptide Science (1999), Volume Date 1998, 35th, 185-188
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Protein Research Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A symposium report. Trichostatin A, trapoxin A and B [cyclo(L-Aoe-L-Phe-L-Phe-D-Xaa); Aoe = (2S,9S) 2-amino-8-oxo-9,10-epoxydecanoic acid; Xaa = Pip (trapoxin A), Pro (trapoxin B)] are known as inhibitors of histone deacetylase (HDAC). Trichostatin A is a reversible inhibitor with hydroxamic acid functionality, and trapoxin A and B are irreversible inhibitors with epoxy ketone group at the side chain of Aoe. On the other hand, Cyl-1, cyclo(L-Aoe-D-Tyr(Me)-L-Ile-L-Pro), was discovered as an inhibitor of the root growth of lettuce seedlings. Since the structure of Cyl-1 resembles trapoxin B, the authors synthesized various Cyl-1 analogs where L-Aoe is substituted by amino acids containing an hydroxamic acid in the side chain, such as L-Asu(NHOH).

IT 90965-62-1DP, Cyl-1, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of hydroxamic acid-containing Cyl-1 analogs as inhibitors of histone deacetylase)

RN 90965-62-1 HCAPLUS

CN Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-L-prolyl] (CA INDEX NAME)



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7
IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(cyclic; synthesis of hydroxamic acid-containing Cyl-1 analogs as inhibitors of histone deacetylase)
IT Hydroxamic acids
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of hydroxamic acid-containing Cyl-1 analogs as inhibitors of histone deacetylase)
IT 90965-62-1DP, Cyl-1, analogs 221186-60-3P
221186-64-7P 221186-71-6P 221186-72-7P
221186-73-8P 221186-74-9P 234123-22-9P
234123-23-0P 234123-24-1P 234123-25-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis of hydroxamic acid-containing Cyl-1 analogs as inhibitors of histone deacetylase)
IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synthesis of hydroxamic acid-containing Cyl-1 analogs as inhibitors of histone deacetylase)
IT 58880-19-6, Trichostatin A 133155-89-2, Trapoxin A
133155-90-5, Trapoxin B
RL: MSC (Miscellaneous)
(synthesis of hydroxamic acid-containing Cyl-1 analogs as inhibitors of histone deacetylase)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 33 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:353256 HCAPLUS Full-text
DOCUMENT NUMBER: 131:130252
TITLE: Histone deacetylase inhibitors based on trapoxin B
AUTHOR(S): Tomizaki, Kin-Ya; Kato, Tamaki; Nishino, Norikazu; Yoshida, Minoru; Komatsu, Yasuhiko
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of

Engineering, Kyushu Institute of Technology, Kitakyushu, 804-8550, Japan
SOURCE: Peptide Science (1999), Volume Date 1998, 35th, 181-184
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Protein Research Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English

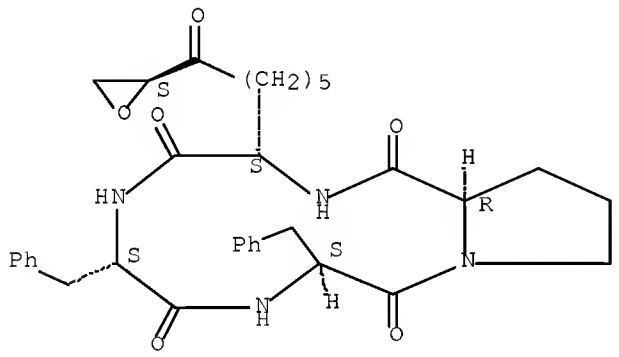
AB A symposium report. Trapoxin B is a cyclic tetrapeptide containing a unique amino acid, (2S,9S)-2-amino-8-oxo-9,10-epoxydecanoic acid (L-Aoe), whose epoxyketone moiety is supposed to react with mammalian histone deacetylase. The authors synthesized a trapoxin B analog, in which L-Aoe is replaced with L-aminosuberic hydroxamic acid [Asu(NHOH)]. The analog strongly inhibited a histone deacetylase from mouse B16/BL6 cells. Furthermore, the positions of D-amino acids in the trapoxin B hydroxamic acid analog were changed. In addition to L-L-L-D-form [containing L-Asu(NHOH)], L-L-D-L-, L-D-L-L-, and L-D-L-D-isomers were synthesized. The L-D-L-L- and L-D-L-D-isomers exhibited high inhibitory activity, while L-L-D-L-isomer was inactive.

IT 133155-90-5D, Trapoxin B, analogs containing aminosuberic hydroxamic acid derivative
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of hydroxamic analogs of trapoxin B as inhibitors of histone deacetylase)

RN 133155-90-5 HCAPLUS

CN Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-L-phenylalanyl-L-phenylalanyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7

ST trapoxin B hydroxamic analog prepn inhibitor histone deacetylase symposium

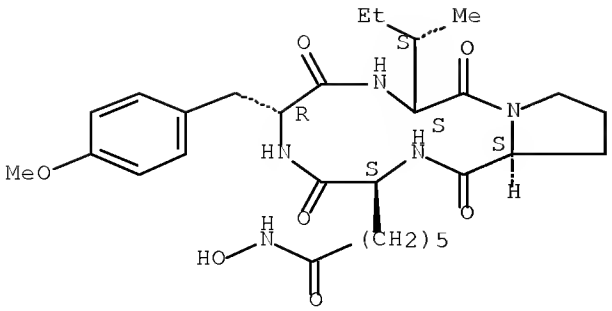
IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cyclic; preparation of hydroxamic analogs of trapoxin B as inhibitors of histone deacetylase)

IT Hydroxamic acids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(peptidyl; preparation of hydroxamic analogs of trapoxin B as inhibitors of

histone deacetylase)
IT 58880-19-6, Trichostatin A 133155-90-5D, Trapoxin B, analogs containing aminosuberic hydroxamic acid derivative 221186-39-6 221186-42-1 221186-43-2 221186-56-7 221186-57-8 221186-58-9 221186-59-0 221186-62-5 234429-76-6 234429-77-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of hydroxamic analogs of trapoxin B as inhibitors of histone deacetylase)
IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of hydroxamic analogs of trapoxin B as inhibitors of histone deacetylase)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 34 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:353220 HCAPLUS Full-text
DOCUMENT NUMBER: 131:116496
TITLE: Conformational analysis of non-natural LDLD-type Cyl-1 analog with high activity
AUTHOR(S): Kato, Tamaki; Tomizaki, Kin-Ya; Tsukamoto, Makiko; Nishino, Norikazu; Yoshida, Minoru; Komatsu, Yasuhiko
CORPORATE SOURCE: Department of Applied Chemistry, Faculty of Engineering, Kyushu Institute of Technology, Kitakyushu, 804-8550, Japan
SOURCE: Peptide Science (1999), Volume Date 1998, 35th, 41-44
CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER: Protein Research Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyl-1 hydroxamic acid analogs, cyclo[-L-Asu(NHOH)-D-Tyr(Me)-L-Ile-(L- and D-)Pro-] (Asu = aminosuberic acid), are inhibitors of histone deacetylase (HDAC). The inhibitory activities of LDLL-type and LDLD-type analogs against HDAC are almost same (IC50 = 3.3 nM). NMR expts. in DMSO-d at room temperature and mol. mechanics calcn. show that the side chain conformation of non-natural LDLD-type analog is similar to that of natural LDLL-type analog in spite of the difference in configurations. This conformational resemblance of the two analogs will explain why the inhibitory activities of these analogs are almost same.
IT 221186-60-3
RL: PRP (Properties)
(conformational anal. of LDLL- and LDLD-types of Cyl-1 hydroxamic acid analogs)
RN 221186-60-3 HCAPLUS
CN Cyclo[(2S)-2-amino-8-(hydroxyamino)-8-oxooctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-L-prolyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7, 22
IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(conformational anal. of Cyl-1 hydroxamic acid analogs, inhibitors of histone deacetylase)
IT 221186-60-3 221186-64-7
RL: PRP (Properties)
(conformational anal. of LDLL- and LDLD-types of Cyl-1 hydroxamic acid analogs)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

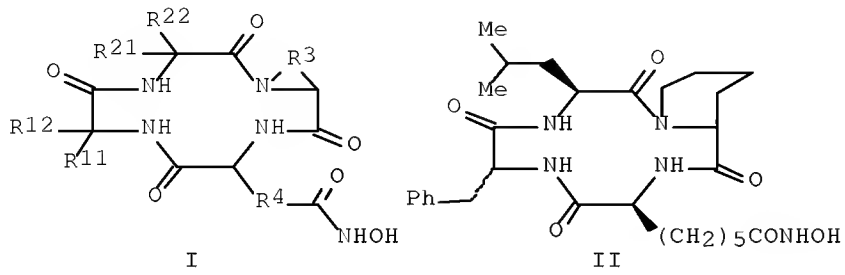
L17 ANSWER 35 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:184270 HCAPLUS Full-text
DOCUMENT NUMBER: 130:237885
TITLE: Preparation of novel cyclic tetrapeptide derivatives as histone deacetylase inhibitors and MHC class-1 molecule expression promoters
INVENTOR(S): Nishino, Norikazu; Yoshida, Minoru; Horinouchi, Sueharu; Komatsu, Yasuhiko; Mimoto, Tsutomu
PATENT ASSIGNEE(S): Japan Energy Corporation, Japan
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911659	A1	19990311	WO 1998-JP3893	19980901
W: AU, CA, JP, KR, NO, NZ, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2302451	A1	19990311	CA 1998-2302451	19980901
AU 9888885	A	19990322	AU 1998-88885	19980901
AU 732299	B2	20010412		
EP 1010705	A1	20000621	EP 1998-940649	19980901
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 503061	A	20010831	NZ 1998-503061	19980901
JP 3494624	B2	20040209	JP 2000-508697	19980901
ZA 9808023	A	19990302	ZA 1998-8023	19980902

NO 2000001045	A	20000427	NO 2000-1045		20000301
US 6399568	B1	20020604	US 2000-486783		20000301
PRIORITY APPLN. INFO.:			JP 1997-237481	A	19970902
			JP 1998-63270	A	19980313
			WO 1998-JP3893	W	19980901

OTHER SOURCE(S): MARPAT 130:237885

GI



I II

AB Claimed are cyclic tetrapeptide derivs. represented by general formula (I) or pharmaceutically acceptable salts thereof and cyclic tetrapeptide compds. analogous thereto [wherein R11, R12, R21 and R22 represent each hydrogen or a monovalent group selected from linear or branched C1-6 alkyl, benzyl, 4-methoxybenzyl, 3-indolylmethyl, (N-methoxy-3-indolyl)methyl, (N-formyl-3-indolyl)methyl, etc.; R3 represents a divalent group selected from divalent linear C3-4 hydrocarbyl optionally having a branched chain added thereto or optionally substituted by a heteroatom; and R4 represents a divalent group derived from divalent linear C4-6 hydrocarbyl optionally having a branched chain added thereto]. Also claimed are histone deacetylase inhibitors, MHC class-1 mol. expression promoters, and anticancer agents containing these cyclic tetrapeptide derivs. as the active ingredient. The hydroxamic acid side chain is responsible for the activity of MHC class-1 mol. expression promotion. These cyclotetrapeptides markedly promote the removal of cancer cells by immune cells using promotion of MHC-1 mol. expression, since they also inhibit cell proliferation and cell cycles, thereby the expansion of cancer tissues, based on histone deacetylase inhibition. They are much more reduced in undesirable side-effects such as cell proliferation inhibition and cell cycle inhibition against normal cells as compared to irreversible enzyme inhibitors, since histone deacetylase enzyme inhibition is reversible. Thus, the title peptide (II) was prepared via deprotection of Boc-Asu(OBzl)-D-Phe-Leu-DL-Pip-OtBu (Asu = α-aminosuberic acid residue, Pip = 2-carboxypiperidine residue) (preparation given), cyclization, and conversion of the side-chain carboxylic acid into hydroxyaminocarbonyl group. II at 3.86 nM in vitro promoted twice the expression of MHC-1 mol. in mouse melanoma B16/BL6 cells as compared to 3.35 nM for trichostatin A and showed IC50 of 12.3 nM against the proliferation of B16/BL6 cells as compared to 14.3 nM for trichostatin A.

IT 221186-39-6P

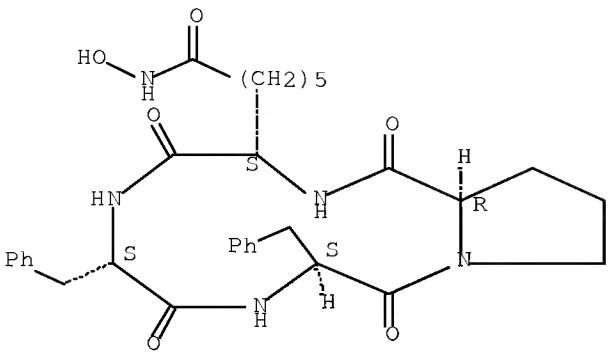
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors and MHC class-1 mol. expression promoters and anticancer agents)

RN 221186-39-6 HCAPLUS

CN Cyclo[(2S)-2-amino-8-(hydroxyamino)-8-oxooctanoyl-L-phenylalanyl-L-

phenylalanyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry.



IC ICM C07K005-12
ICS A61K038-12
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST cyclic tetrapeptide prepn histone deacetylase inhibitor; MHC1 mol expression promoter; anticancer cyclotetrapeptide prepn
IT Antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(MHC class-1 mol.; preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors and MHC class-1 mol. expression promoters and anticancer agents)
IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors and MHC class-1 mol. expression promoters and anticancer agents)
IT Antitumor agents
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors and MHC class-1 mol. expression promoters and anticancer agents)
IT 221186-39-6P 221186-42-1P 221186-43-2P
221186-44-3P 221186-45-4P 221186-46-5P
221186-47-6P 221186-48-7P 221186-49-8P
221186-50-1P 221186-51-2P 221186-52-3P
221186-53-4P 221186-54-5P 221186-55-6P 221186-56-7P
221186-57-8P 221186-58-9P 221186-59-0P
221186-60-3P 221186-61-4P 221186-62-5P
221186-64-7P 221186-65-8P 221186-66-9P
221186-67-0P 221186-68-1P 221186-69-2P
221186-70-5P 221186-71-6P 221186-72-7P
221186-73-8P 221186-74-9P 221186-75-0P
221186-76-1P 221186-77-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors and MHC class-1 mol. expression promoters and anticancer agents)

IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors and MHC class-1 mol. expression promoters and anticancer agents)

IT 79-08-3, Bromoacetic acid 107-18-6, 2-Propen-1-ol, reactions 108-24-7 338-69-2, D-Alanine 1161-13-3 2018-66-8 2419-94-5 2448-45-5 2812-46-6 2916-68-9, 2-Trimethylsilylethanol 3392-05-0 5470-11-1, Hydroxylamine hydrochloride 13139-16-7 13734-34-4 13734-34-4D, oxime resin-bound 15030-72-5 15761-39-4 18942-49-9 18942-49-9D, oxime resin-bound 24424-99-5, Di-tert-butyl dicarbonate 53267-93-9 53843-90-6, D-Proline benzyl ester hydrochloride 68856-96-2, Boc-D-Tyr(Me)-OH 90071-62-8 147202-35-5 174784-95-3 174784-95-3D, oxime resin-bound 221187-38-8 221187-38-8D, oxime resin-bound 221187-40-2 221187-40-2D, oxime resin-bound
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors and MHC class-1 mol. expression promoters and anticancer agents)

IT 73998-02-4P 92050-62-9DP, oxime resin-bound 162757-06-4P 221186-78-3P 221186-79-4P 221186-80-7P 221186-81-8P 221186-83-0P 221186-84-1P 221186-85-2P 221186-86-3P 221186-87-4P 221186-88-5P 221186-89-6P 221186-90-9P 221186-91-0P 221186-92-1P 221186-93-2P 221186-94-3P 221186-96-5P 221186-97-6P 221186-98-7P 221186-99-8P 221187-00-4P 221187-01-5P 221187-02-6P 221187-03-7P 221187-04-8P 221187-05-9P 221187-06-0P 221187-07-1P 221187-08-2P 221187-09-3P 221187-10-6P 221187-11-7P 221187-12-8P 221187-13-9P 221187-15-1P 221187-17-3P 221187-19-5DP, oxime resin-bound 221187-21-9DP, oxime resin-bound 221187-21-9P 221187-25-3P 221187-27-5P 221187-29-7DP, oxime resin-bound 221187-29-7P 221187-32-2DP, oxime resin-bound 221187-33-3DP, oxime resin-bound 221187-34-4DP, oxime resin-bound 221187-35-5DP, oxime resin-bound 221187-36-6DP, oxime resin-bound 221187-37-7DP, oxime resin-bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of novel cyclic tetrapeptide derivs. as histone deacetylase inhibitors and MHC class-1 mol. expression promoters and anticancer agents)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 36 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:468977 HCAPLUS Full-text
DOCUMENT NUMBER: 127:162081
ORIGINAL REFERENCE NO.: 127:31431a,31434a
TITLE: Analogs of trichostatin A and trapoxin B as histone deacetylase inhibitors
AUTHOR(S): Jung, Manfred; Hoffmann, Katharina; Brosch, Gerald; Loidl, Peter
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Munster, Munster, 48149, Germany
SOURCE: Bioorganic & Medicinal Chemistry Letters (1997), 7(13), 1655-1658
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier

DOCUMENT TYPE: Journal
LANGUAGE: English

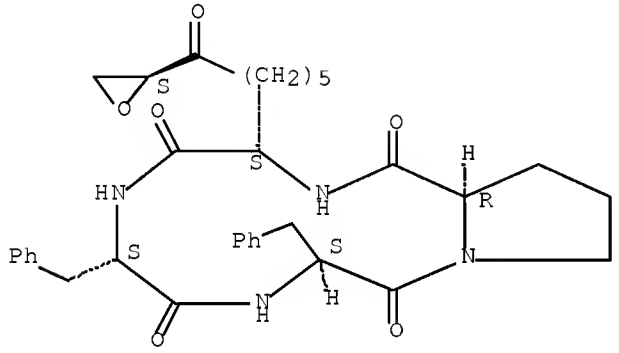
AB Inhibitors of histone deacetylase are potent inducers of differentiation and bear considerable potential as drugs for chemoprevention and treatment of cancer. So far only complex natural products and a few synthetic congeners have been identified as specific inhibitors. A set of simple analogs was prepared in as little as four synthetic steps that have inhibitory potencies in the range of known cyclotetrapeptide inhibitors. These compds. are interesting leads for the design of potent inhibitors of histone deacetylase.

IT 133155-90-5DP, Trapoxin B, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of trichostatin A and trapoxin B analogs as histone deacetylase inhibitors)

RN 133155-90-5 HCAPLUS

CN Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-L-phenylalanyl-L-phenylalanyl-D-prolyl] (CA INDEX NAME)

Absolute stereochemistry.



CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7, 25

ST trichostatin A analog histone deacetylase inhibitor; trapoxin B analog histone deacetylase inhibitor; carboxamide hydroxamate prepn histone deacetylase inhibitor

IT 64-04-0P, Phenethylamine 3196-73-4P, β-Alanine methyl ester hydrochloride 193550-97-9P 193550-99-1P 193551-05-2P 193551-06-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of trichostatin A and trapoxin B analogs as histone deacetylase inhibitors)

IT 58880-19-6DP, Trichostatin A, analogs 133155-90-5DP, Trapoxin B, analogs 193550-93-5P 193550-95-7P 193550-98-0P 193551-00-7P 193551-02-9P 193551-04-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of trichostatin A and trapoxin B analogs as histone deacetylase inhibitors)

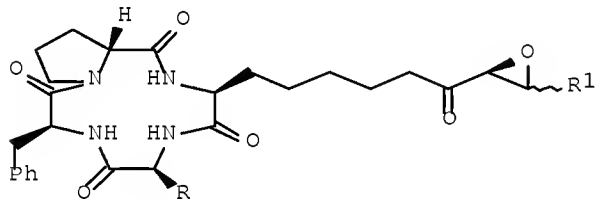
IT 9076-57-7, Histone deacetylase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of trichostatin A and trapoxin B analogs as histone deacetylase inhibitors)

IT 619-84-1, p-(Dimethylamino)benzoic acid 1926-80-3, 6-Aminohexanoic acid methyl ester hydrochloride 3946-32-5, Octanedioic acid monomethyl ester 7524-50-7, Phenylalanine methyl ester hydrochloride 7536-58-5 29588-83-8, N-Phthalyl-D-alanine 37784-17-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of trichostatin A and trapoxin B analogs as histone deacetylase inhibitors)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 37 OF 37 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1996:616695 HCAPLUS Full-text
DOCUMENT NUMBER: 126:8585
ORIGINAL REFERENCE NO.: 126:1911a,1914a
TITLE: Synthesis of Natural and Modified Trapoxins, Useful Reagents for Exploring Histone Deacetylase Function
AUTHOR(S): Taunton, Jack; Collins, Jon L.; Schreiber, Stuart L.
CORPORATE SOURCE: Howard Hughes Medical Institute, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Journal of the American Chemical Society (1996), 118(43), 10412-10422
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Trapoxin B (I; R = CH2Ph, R1 = H), a cyclotetrapeptide isolated from the fungus Helicoma ambiens, profoundly affects mammalian cell growth and morphol. In this paper, the syntheses of trapoxin B, [3H]trapoxin B (I; R = CH2Ph, R1 = T), and K-trap [I; R = (CH2)4NHAlloc,R1 = H], a trapoxin-based affinity reagent are described. These reagents allowed the first mol. characterization of histone deacetylase, the cellular target of trapoxin B.

IT 183609-96-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of natural and modified trapoxins as useful reagents for exploring histone deacetylase function)

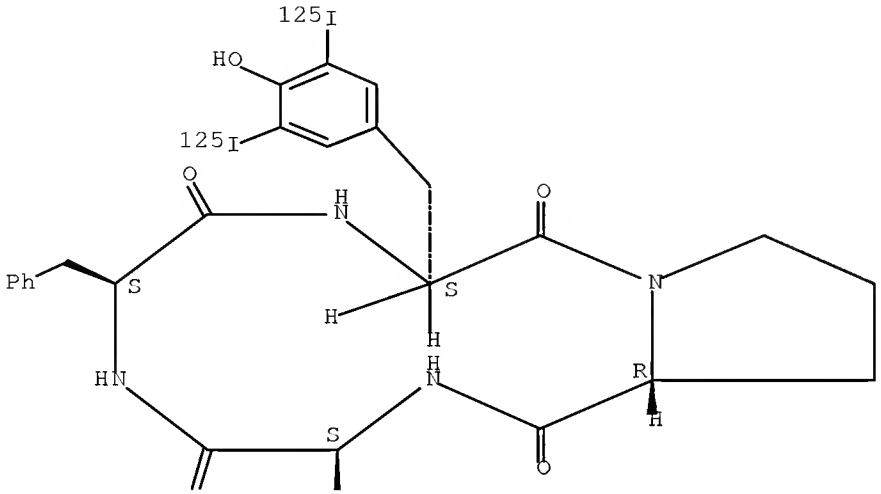
RN 183609-96-3 HCAPLUS

CN Cyclo[(αS,2S)-α-amino-η-oxooxiraneoctanoyl-L-phenylalanyl-

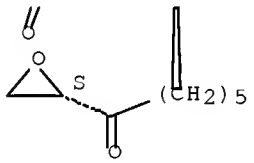
3,5-di(iodo-125I)-L-tyrosyl-D-prolyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 9

ST trapoxin B cyclotetrapeptide analog prepn; histone deacetylase characterization trapoxin analog

IT 60454-66-2DP, Affi-Gel 10, reaction products with trapoxin B lysine side chain derivative 183609-96-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of natural and modified trapoxins as useful reagents for exploring histone deacetylase function)

IT 9076-57-7, Histone deacetylase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of natural and modified trapoxins as useful reagents for exploring histone deacetylase function)

IT 4224-70-8, 6-Bromohexanoic acid 13734-34-4 26054-60-4 50622-09-8, (+)-2,3-O-Isopropylidene-L-threitol 54314-84-0, Benzyl 3-bromopropyl ether 90719-32-7, (S)-4-Benzyl-2-oxazolidinone 104669-73-0 183609-55-4 183610-02-8

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of natural and modified trapoxins as useful reagents for exploring histone deacetylase function)

IT 108817-96-5P 183609-58-7P 183609-61-2P 183609-64-5P 183609-68-9P
183609-73-6P 183609-77-0P 183609-79-2P 183609-81-6P
183609-83-8P 183609-84-9P 183609-85-0P 183609-86-1P
183609-87-2P 183609-88-3P 183609-89-4P 183609-90-7P
183609-91-8P 183609-93-0P 183609-95-2P
183609-98-5P 183609-99-6P 183610-00-6P 183610-01-7P
183610-03-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of natural and modified trapoxins as useful reagents for exploring histone deacetylase function)

IT 133155-90-5P 183609-51-0P 183609-94-1DP,
lysine side chain amides with Affi-Gel 10
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of natural and modified trapoxins as useful reagents for exploring histone deacetylase function)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

******* SEARCH HISTORY *******

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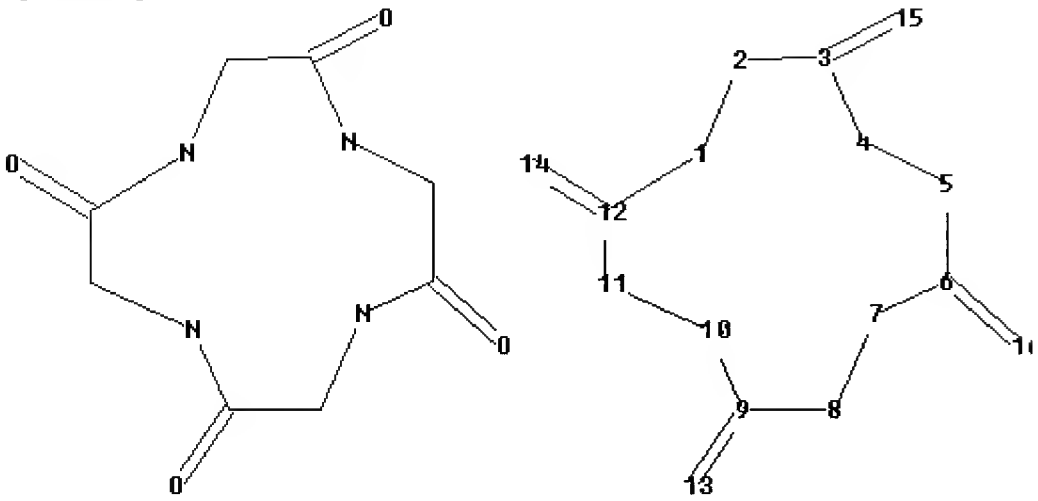


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ring nodes :
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ring bonds :
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exact/norm bonds :
1-2  1-12  2-3  3-4  3-15  4-5  5-6  6-7  6-16  7-8  8-9  9-10  9-13  10-11  11-12
12-14


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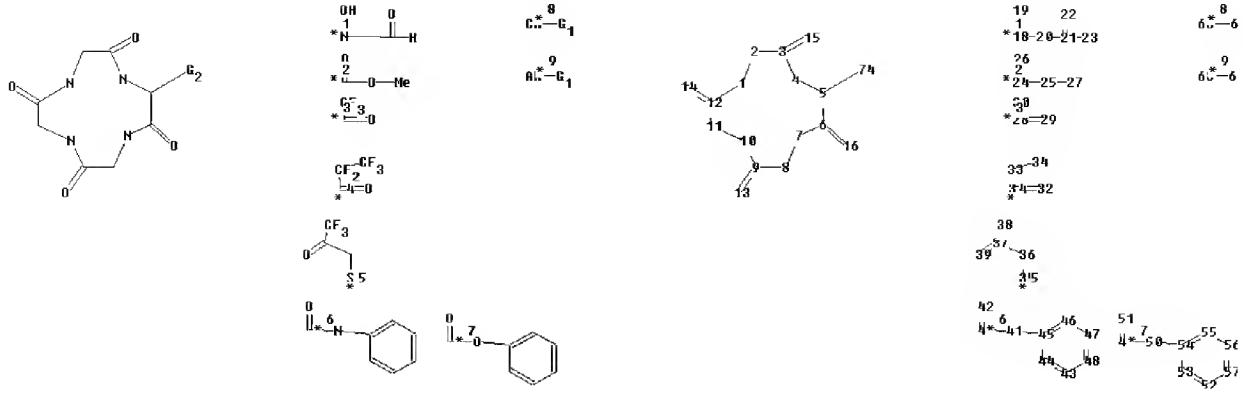

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50-54 66-67 68-69
ring bonds :
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containing 43 : 52 :

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G2:[*8],[*9]

Match level :
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